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RENAL COUNTERBALANCE *

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Attention to the processes involved in renal counterbalance will tend to stimulate a search by both surgeon and clinician for better tests of renal function than are now available, and mutual benefit will result. A closer correlation by both groups of practitioners of the so-called surgical and medical lesions of the kidney is desirable. The surgical specialist cannot safely separate his field from the conservative eye of the internist, and in many nephritides joint study also is desirable. Renal function constitutes a work bench already equally familiar and important, and a more thorough conception of renal counterbalance in its relation to medical and surgical diseases of the kidney will tend to destroy the artificiality of their separation as well as to increase the value of functional studies themselves.

In 1922, an experimental consideration of renal counterbalance was presented before the American Association of Genito-Urinary Surgeons, but the published record in the transactions of this meeting is so full of errors, due to changes from deletion of illustrations originally submitted and the inability of the writer at that time properly to correct the proof, as to justify another presentation in a fuller form. This attempt is further stimulated by the amount of general interest that has been shown during the last two years in the first defective effort, and this interest seems to warrant publication of the present fuller and corrected manuscript in a medical journal of more general circulation.

INTRODUCTION

The subject of compensatory renal hypertrophy has by no means been entirely neglected. Rayer,[1] as early as 1841, gives in his remarkable textbook as good a clinical description as has since appeared. Albarran's [2] contributions are commendable, and various aspects have been discussed by others; in fact, its recognition has become so general as nowadays to attract little notice or comment. Remove or injure one kidney, and it is known that in most instances the other will hypertrophy.

* Read before the Kansas City Clinical Society, Oct. 14, 1924.

1. Rayer: Traité des Maladies des reins, Paris, **3**, 1841.

2. Albarran, J.: L'hypertrophie compensatrice en pathologie rénale, Presse méd. **7**:85 (Feb. 22) 1899.

To the surgeon, the choice between certain operative procedures is often difficult, in spite of improvement in the methods of diagnosis and in surgical technic. Mistakes by no means approach the frequency of their occurrence prior to the common use of the cystoscope, ureteral catheterization and functional tests. But occasionally every surgeon practicing in the field of the urinary tract will meet with a surprise and wish, when it is too late, that in place of being conservative he had been radical, or vice versa. Some of these surgical failures can be justly attributed to faulty technic, but others cannot be so easily explained, and it is in this latter group that a more thorough understanding of the processes of renal counterbalance is needed.

To the clinician, a number of problems have a close relationship to renal counterbalance, particularly studies of function. The tests of renal activity are deficient in many ways. They have little value prognostically, and the poorly understood factors behind renal inhibition render them difficult of interpretation diagnostically. Many experienced clinicians prefer the information of the bedside to the laboratory. Too frequently the two are impossible of correlation, pure nephrosis being the conclusion of clinical indications counter to a definite picture of nephritis by the laboratory. Conciliation of factors of renal activity and inactivity with those of stimulation and inhibition will help to clarify tests of function, and the factors of compensation are inseparable from the problem. It is well known that a full diet in bilateral nephritis will often give renal stimulation, which results in group hypertrophy and better function, and thus will be preferable to the limitation of food and renal rest.

DEFINITION

The anatomic division of the renal mass into equal and separate portions, a right and left kidney, and the fact that injury is commonly unilateral and is seldom diffuse and uniform, even when bilateral, are the two basic principles which establish the clinical and surgical importance of renal counterbalance. The law of supply and demand, in the economics of industry, may serve in point of illustration. The total renal mass and total renal function represent an equilibrium of supply and demand. Small animals have small kidneys, and large animals have relatively larger kidneys, proportional to the amount of work required. The demand or total work varies in general with the growth of the individual and with the normal fluctuations of excretion following changes in diet and exercise. But the supply, or renal mass that performs the required work, may show secondary alterations. Usually, such acquired changes are those of loss or insufficiency of renal mass as a result of disease, trauma or operation, and are commonly unilateral or affect circumscribed portions. Occasionally, the acquired change may

give a surplus of renal supply over the more or less constant functional demand, as after the removal of ureteral stones, repair operations in hydronephrosis or the subsidence of infectious, or of other group injury in which there has been hypertrophy of one and slight damage of the other side. The establishment of a new equilibrium of renal supply and functional demand following these acquired alterations is the process of renal counterbalance. An anatomic readjustment may take years for completion, even though functional compensation, as indicated by tests of total function, is effected within a few days, but, obviously, the anatomic consideration is the more important. Hypertrophy and atrophy are the fundamental factors in this process—reparatory hypertrophy of renal tissue in response to the demand of an increase in functional activity; atrophy of renal tissue, primarily degenerative in most cases but occasionally functional in character as a result of loss of or insufficient stimulation.

PART I. EXPERIMENTAL STUDY

Renal compensation has been experimentally tested from so many different angles that it will be well to present the subject in a systematic way, giving as we go our own work in detail in its proper place. The experimental problem presents four parts for consideration: (1) the reserve power of renal tissue; (2) the reparatory changes of renal tissue as a result of an increase of activity; (3) renal atrophy from retrogressive changes and inactivity, and (4) the counterbalance between these factors.

SECTION I. RENAL RESERVE POWER

1. INTRODUCTION

Reserve force is a prominent characteristic of all living matter in the sense that cells, tissues and organs do not work to their utmost limit. The popular idea conceives a definite reserve of energy over and above that ordinarily required as a result of the force of "physiologic inertia" which has led to an overadjustment. When the cell assimilates, it continues to assimilate more than is actually needed, and when it starts to grow, it continues to grow beyond the extent of the initial stimulus. An interesting and somewhat different speculation regarding the reserve power possessed by all organs, more substance than is necessary to do their ordinary work, lies in the conception that the units of which an organ is composed are not all active at the same time during ordinary activity of the organ, but that each unit, when active, acts to its utmost capability, so that variations in the total activity correspond to a proportional variation in the number of active units. A low function requires the activity of relatively few units as compared to the number called into activity by a high function, whereas an unusual or marked

requirement might call all units into activity. This idea is particularly attractive with reference to the kidney with its 2,000,000 or so units. Each unit, when active, does as much as it is capable of and shows a "refractory" period, as in that of heart muscle, followed by an interval of rest, during which other units are carrying on the total work of the organ. When the amount of work to be accomplished is increased, an increased number of units are thrown into activity, and there is not an increased activity of already active units (Khanolkar).[3] Reserve, in this sense, is with respect to numbers of units of an organ and not to the potential powers of each.

In any event, it has long been known that normally more renal tissue is supplied than is absolutely required. This reserve, however, cannot be regarded as unnecessary. Its purpose is to safeguard against the need of an occasional overload, and it probably is developed in consequence of such variation, on the same sound principle used in the construction of a bridge to carry several times the load expected of it.

Consideration of this reserve power shows that functional and anatomic conditions are nicely balanced. The functional margin of safety has its anatomic counterpart, as is shown by the changes of structure in the remaining kidney after nephrectomy (described later). The anatomic condition, within certain limitations, will undergo change in proportion to the functional demand. Tests of renal function, however, are wofully deficient in respect to this interdependence, and although we realize well enough the value of correlation of structure with function, this correlation is impossible with our present known tests. We may have evidence of normal function and find anatomic deficiency, or we may have evidence of functional insufficiency and find normal structure. Inhibition of one without inhibition of the other may occur. So that, in spite of the fact of the existence of a relative proportion between excretory power and mass of excreting substance (Schwarz,[4] Addis[5]), inefficient methods of study render of no practical use the separation of a functional and anatomic reserve, although, theoretically, separate consideration is advisable.

2. ANATOMIC RESERVE

The proportion of renal mass to body weight is normally very uniform for animals of the same or similar species. For example, the average weight of the kidneys in cats is 9.1 gm. per kilogram, and in

3. Khanolkar, V. R.: Partial Activity of the Kidney and the "All or Nothing" Principle, J. Path. & Bacteriol. **25**:414-424 (Oct.) 1922.

4. Schwartz, O.: Ueber die sogenannte "Reservekraft" der Niere, Ztschr. f. Urol. **13**:127, 1919.

5. Addis, T.: Renal Function and Amount of Functioning Tissue, Arch. Int. Med. **30**:378-385 (Sept.) 1922.

dogs 6.7 gm. per kilogram (Bainbridge and Beddard [6]). If it were possible to alter the amount of renal mass, the functional demand remaining constant, without change, such, for instance, as hypertrophy of the remaining renal tissue after some of that normally present has been removed, or atrophy in the case of an addition to the renal mass, then the amount of renal tissue possible of removal without an hypertrophy of that left behind would measure the actual anatomic reserve, and the amount of renal tissue added without atrophy following would be the maximum anatomic reserve possible. Obviously, relative degrees of hypertrophy and of atrophy would be extremely difficult if not impossible of measurement, and there is no experimental or other evidence of an actual surplus of renal tissue over and above the physiologic reserve normally present.

(*a*) *Minimal Amount of Renal Tissue Compatible with Life.*—The minimal amount of renal parenchyma necessary for the continuation of life as well as of normal function is easier of determination. De Paoli,[7] in 1892, by resection of part of a kidney and nephrectomy on the other side, found that an animal could live on one-half of one kidney, or one-fourth of the total mass. Paoli Fiori [8] (1901), by similar experiments, estimated the amount of kidney substance necessary to support life in a dog as from 1.12 to 1.18 gm. per kilogram of the body weight of the animal. (The normal proportion is from 6 to 7 gm. per kilogram.) Castaigne.[9] (1902) determined that from one-third to one-fourth of the combined kidney weight is necessary for life. Vitzou [10] obtained a similar result. Mauchle [11] (1894) reached the same general result after nephrectomy on one side and ligature of several of the smaller branches of the opposite renal artery; and Pilcher [12] (1913) reduced the kidney substance, also by ligature of branches of the renal artery, to one-fourth and found that the urine

6. Bainbridge and Beddard: The Relation of the Kidneys to Metabolism; Preliminary Communication, Proc. Roy. Soc., London, Series B, **79**:75, 1907.

7. De Paoli: Della Resezione del rene, Zentralbl. f. Chir. **19**:78, 1892.

8. Fiori, Paolo: L'ipertrofia anatomica e funzionale del rene e la tolleranza dell'organismo nelle demolizioni estese dell' organo, Policlinico **8**:349-370; 428-488, 1901.

9. Castaigne and Rathery: Lesions experimentales de l'epithelium des tubes contournes, Compt. rend. Soc. de biol. **54**:565-567, 1902.

10. Vitzou, A. N.: Effects de l'extirpation partielle d'un rein suivie, un mois apres de l'extirpation de l'autre, Compt. rend. Soc. de biol. **53**:1167-1169, 1901.

11. Mauchle: Beitr. zur Kentniss der compensatorischen Hypertrophie der Nieren, Zurich, 1894.

12. Pilcher, J.: On the Excretion of Nitrogen Subsequent to Ligation of Successive Branches of Renal Arteries, J. Biol. Chem. **14**:389, 1913.

remained normal in quantity. Tuffier [13] found 1.5 gm. of kidney substance per kilogram sufficient to maintain life. Rose-Bradford [14] caused death in from one to six weeks by removal of three fourths of the renal substance, and this finding has been confirmed by Bainbridge and Beddard.[6] More recently, Karsner, Bunker and Grabfield [15] (1915) have been able to reduce the renal mass by two-thirds without affecting the normal amount and concentration of urine excretion. Pearce,[16] Tuffier,[13] Paoli Fiori [8] and others, by allowing compensatory hypertrophy to occur after the removal of half a kidney, both before and after opposite nephrectomy, were then able to remove still more, sometimes as much as three-fourths of the total kidney substance in dogs and rabbits without change in the nitrogen metabolism. Tuffier and Paoli Fiori even state that, by partial successive resections, they have been able to remove a quantity of renal tissue of which the weight was only a little less than the normal total weight of two kidneys. To quote the latter:

> I succeeded in keeping alive dogs in which I had removed almost the total original weight of the two kidneys, and this in a relatively short interval; in fact, in Experiment 9, a dog weighing 4,500 gm., I removed in an interval of forty-five days a quantity of renal tissue equal to 25 gm. out of an original total of 26 gm.; in a dog weighing 8,000 gm. (Experiment 11) I succeeded in excising 39 gm. out of an original total of 40 gm. in an interval of thirty-six days.

Table 1 gives in actual figures the minimal amount of renal parenchyma necessary for renal function and the maintenance of life.

Although these uniform results from so many different sources demonstrate that the minimal amount of renal tissue required is about one-third of the normal amount supplied, they do not prove that two-thirds of the renal mass is carried as a surplus, or static reserve. On the contrary, they demonstrate the remarkable compensatory power of normal renal tissue, for it has been a common observation that the one-third portion, left to do all the work, undergoes hypertrophy. This remnant is able by an anatomic hypertrophy to treble its functional power. It now works under great stress, however, and the functional conditions of the hypertrophic one-third portion and two normal kidneys are in no way comparable. An extra burden would be easily carried by the latter but would quickly overwhelm the former, already working at its maximum.

13. Tuffier, M.: Nephrectomie et resection partielles du rein—Pathologie experimentale, Bull. Soc. anat. de Paris **63**:447, 1888.

14. Rose-Bradford, J.: The Results Following Partial Nephrectomy and the Influence of the Kidney on Metabolism, J. Physiol. **23**:415-496, 1899.

15. Karsner, Bunker and Grabfield: A Note on the Immediate Effects of Reduction of Kidney Substance, J. Exper. Med. **22**:544, 1915.

16. Pearce: The Influence of the Reduction of Kidney Substance upon Nitrogenous Metabolism, J. Exper. Med. **10**:632, 1908.

Anatomic reserve, according to this conception, is measured by the ability to grow. When this fails, there is no reserve. It may therefore be considered as of two types:

1. Native: The anatomic reserve power of normal tissue.

2. Compensatory: The anatomic reserve of tissue which has undergone reparation.

3. FUNCTIONAL RESERVE

(*a*) *Amount of Overload Without Hypertrophy.*—The exact parallelism of structure and function is open to question in considering functional reserve. Is it possible for renal tissue to hyperfunction without undergoing proportionate hypertrophic changes? Such a possibility might be tested by subjecting kidneys to a continuous and known overload. No subsequent anatomic change would be evidence of a

TABLE 1.—*Minimal Amount of Renal Parenchyma Required for Renal Function and Life (Paoli Fiori)*

Animal	Weight	Absolute Quantity	Quantity per Kilogram
Resection on One Side Followed by Opposite Nephrectomy			
Rabbit	1,250 gm.	From 3.0 to 3.5 gm.	2.30 gm.
Rabbit	1,600 gm.	3.5 to 3.8 gm.	1.90 to 2 gm.
Dog	5,000 gm.	9.0 gm.	1.70 to 1.80 gm.
Dog	7,500 gm.	10.0 to 10.50 gm.	1.38 to 1.40 gm.
Nephrectomy Followed by Resection			
Rabbit	1,500 gm.	From 5.0 to 5.5 gm.	3.5 gm.
Rabbit	1,450 gm.	4.0 to 4.5 gm.	3.40 gm.
Dog	6,000 gm.	9.0 to 9.5 gm.	1.3 to 1.4 gm.
Dog	6,800 gm.	11.0 to 12.0 gm.	1.7 to 1.8 gm.
Dog	4,500 gm.	5.5 gm.	1.22 gm.
Dog	8,000 gm.	9.0 to 9.5 gm.	1.12 to 1.18 gm.

static functional reserve. Emge [17] subjected the kidneys of white rats to a markedly prolonged strain in the excretion of urea without producing any noticeable anatomic change in any part of the glomerulotubular apparatus. This result might be taken as an indication either that the static reserve of these kidneys was sufficient to care for the overload or that this type of overload was met by an anatomic change which was overlooked by the investigator. None of the polyurias, either of diabetes mellitus or insipidus or of puncture, produce recognizable changes of growth in the renal structure, nor does a continuous and profuse diuresis (urea, sodium chlorid, diuretin, digitalis [Hinman and Belt [18]] and splanchnotomy [Hinman and Hepler [19]]) influence the rate of development of hydronephrosis, and yet there must be as

17. Emge, L. A.: A Cytological Study of the Kidney Cell in Long Continued Hyperfunction with Relation to Hypertrophy and the Mitochondrial Apparatus, Stanford University Pub. Univ. Series Med. Sc. **1**, No. 2, p. 107, 1921.

18. Hinman, F., and Belt, A. E.: Experimental Hydronephrosis, Failure of Diuresis to Affect Its Rate of Development, J. Urol. **9**:397-419 (May) 1923.

19. Hinman, F., and Hepler, A. B.: Experimental Hydronephrosis: The Effect of Changes of Blood Pressure and Blood Flow on Its Rate of Development, I, Splanchnotomy, Arch. Surg. **11**:578 (Oct.) 1925.

much of an overload, in some of these conditions, as in the diuresis of forced urea feeding. It is possible, therefore, that the changes of growth have either been absent or so insignificant as to be overlooked. That a more general overload produces anatomic changes in both kidneys in every way like that in one after removal of its mate is proved by a number of experiments, which are discussed later under Bilateral Mass Hypertrophy, Section II.

(*b*) *Reserve of Function Before Hypertrophy Has Occurred After Opposite Nephrectomy.*—Another way of testing functional reserve is by the estimation of the renal function of the remaining kidney after nephrectomy, in the period before anatomic growth has had time to occur. The one great objection to most of the experimental work in this line is the failure to note the significance of tests in the early as compared to late periods. Bonardi,[20] for example, found the resistance of animals markedly reduced to bacterial and chemical toxins from twenty-four to forty-eight hours after unilateral nephrectomy, and concludes that persons with one kidney are similarly handicapped. But he failed to study the resistance of his animals after compensatory hypertrophy of the remaining kidney had occurred; probably the animal's resistance to toxins would then be little, if any, reduced. Many observers, when they state that the urine remains normal in concentration and amount after partial resections and nephrectomy, fail to state at what period after operation the tests were made. One cannot help presuming that they were made after sufficient time was allowed for compensatory changes to have occurred.

It is a general belief that the reserve of a healthy kidney is sufficient immediately to cover the loss of its partner, but on more careful study, this proves only partially correct. Karsner, Bunker and Grabfield [15] (1915) followed the nonprotein nitrogen of the blood after reduction of kidney substance and found a distinct increase lasting for three days. After removal of even two thirds of the total kidney substance, the excretion of urine returned to normal in quantity and concentration within this period. Rowntree and Geraghty [21] estimated that from two to three weeks are required after unilateral nephrectomy for phenolsulphonephthalein to be excreted as normally as by two healthy kidneys. Sudden occlusion of one kidney in cats, under diuresis, caused usually a slight fall both in the quantity of urine and phenolsulphonephthalein output, which in some cases, however, remained unchanged.

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20. Bonardi, M.: Influence de la nephrectomie sur la resistance des animaux aux infections et aux empoisonnements, Arch. d. Clin. Med., December, 1892; review by Legram: Ann. d.mal. d. org. génito-urin. **12**:121, 1894.

21. Rowntree, L. G., and Geraghty, J. T.: The Phthalein Test; an Experimental and Clinical Study of Phenolsulphonephthalein in Relation to Renal Function in Health and Disease, Arch. Int. Med. **9**:284-338 (March) 1912.

The relative percentage output of phenolsulphonephthalein twenty-four hours before and twenty-four hours after unilateral nephrectomy, in a dog, is given in Table 2.

By following the fluid and chemical constituents of the urine, Paoli Fiori [22] estimated that ten days are required for complete restoration of function after nephrectomy. And Tuffier [23] similarly estimated a period of six days as necessary for the return of the urine to normal. De Paoli [7] observed definite changes in the urine after nephrectomy, although Sacerdotti [24] found none in six dogs, only two of which showed transitory albuminuria. (Unilateral nephrectomy causes no marked changes in the urine, "Hat die einseitige Nephrectomie keine bedeutende Störung in der Harnsecretion im Gefolge," p. 274). André Weill,[25] however, using Ambard's [26] constant, estimated that it took two months in dogs for the remaining kidney to take over the work of two kidneys.

TABLE 2.—*Output of Phenolsulphonephthalein Before and After Unilateral Nephrectomy in a Dog (Rowntree and Geraghty [21])*

Time after Injection	Percentage Output	
	24 Hours Before	24 Hours After
5 minutes	17	14
10 minutes	32	25
15 minutes	37	30
20 minutes	41	34
25 minutes	46	38
30 minutes	48	40

Weill had previously fed his dogs on meat until the urea concentration in the urine had become maximum and constant, so that, in his experiments, the reserve kidney had to compensate for a distinct overload. Ribbert [27] observed that it took "several days" after nephrectomy for the remaining kidney to be able to excrete indigocarmin in the same time as normal animals, and he made the interesting observation that, in old animals, the remaining kidney never did become able to excrete all the dyestuff in the normal time period. Wossidlo,[28] also with the

22. Fiori, Paolo: Nefrectomia ed uretero-stenosi unilateral, Policlinico **10**:228, 1903.

23. Tuffier, M.: Etudes Experimentales sur la Chirurgie du rein, nephrectomie; nephrorraphie, nephrotomie; ureterotomie, Paris, G. Steinheil, 1889, p. 106.

24. Sacerdotti, C.: Ueber die Compensatorische Hypertrophie der Nieren, Virchows Arch. f. path. Anat. **146**:267-297, 1896; Sulla ipertrofia compensatoria dei reni, Arch. per le Sc. med. **20**:245-276, 1896.

25. Weill, André, cited by O. Schwartz (Footnote 4).

26. Ambard: Ambard's Law, J. Physiol. et Path. gen., **14**:753, 1912.

27. Ribbert: Ueber compensatorische Hypertrophie der Nieren, Virchows Arch. f. path. Anat. **88**:11, 1882.

28. Wossidlo, E.: Zur Funktion der Hypertrophischen Niere, Berl. klin. Wchnschr. **51**:467, 1914.

aid of indigocarmin, found that about six weeks are required for a return to a normal equilibrium after nephrectomy.

With Kutzmann in collaboration,[29] I made carefully controlled experiments in dogs to test this point of functional reserve after nephrectomy, and these tests showed that, in the first two to three days after nephrectomy, the excretions of urea and phenolsulphonephthalein

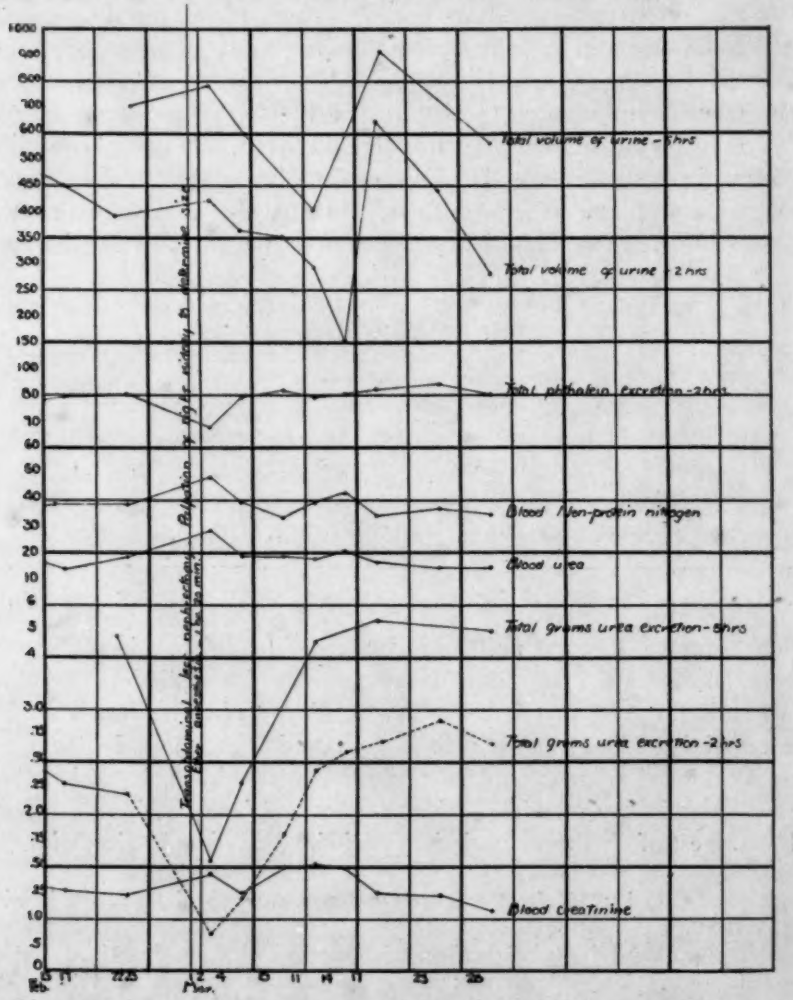
Total volume of urine - 6 hrs
Total volume of urine - 2 hrs
Total phthalein excretion - 2 hrs
Blood Non-protein nitrogen
Blood urea
Total grams urea excretion - 6 hrs
Total grams urea excretion - 2 hrs
Blood creatinine
Feb.
Mar.

Fig. 1.—Functional reserve of one kidney after opposite nephrectomy. The remaining kidney is unable to do the work of two, as shown by simple excretion and retention tests, before from nine to eleven days. Phenolsulphonephthalein output and blood nitrogen are normal on the fifth or sixth days, but response to an overload by urea injection is not equal to that before nephrectomy till from the ninth to eleventh day, and, as shown elsewhere, the functional capability of the hypertrophic kidney never quite equals that of two normal kidneys.

29. Hinman, F., and Kutzmann, O. W., to be published.

are definitely diminished, and that there is a corresponding rise of urea and nonprotein nitrogen in the blood. The findings are reproduced in Figure 1. Phenolsulphonephthalein is normal by the third or fourth day, but urea excretion not until about the tenth or eleventh day. Putting the kidney under a greater strain by injecting urea prolongs the period of unbalance. A control experiment with dogs under ether for one hour, but without nephrectomy, gave no similar alteration in the phenolsulphonephthalein, or in the blood and urine nitrogen.

Some experiments performed for another purpose, in collaboration with Butler,[30] shed information on the subject under consideration. The anterior and posterior branches of the renal artery supply approximately respective halves of the kidney. Ligature of one reduces the active kidney mass by one-half, but, as may be seen by Figure 2, neither the secretory pressures nor functional activity, as measured by phenolsulphonephthalein, are proportionately reduced. There is an immediate compensation for the loss, but only partial. The native reserve of the active half is never able completely to compensate for the 50 per cent. anatomic loss.

In this connection, some unpublished studies of Addis[31] are of interest. The remaining kidney in a rabbit, from three to four months after nephrectomy, as tested by Addis' urea dilution method, which subjects the kidney to an overload of urea, is equivalent to 66 per cent. of the normal of two kidneys. As compensatory hypertrophy is complete within this period, it is probable from this that the compensatory kidney never develops a functional reserve equal to that of two normal kidneys.

The generally accepted idea that a healthy kidney has sufficient reserve of function to cover the loss of its partner is seen to be only partially correct. Ordinary functional ability is recovered after anatomic reparation has occurred, but the reaction of even this compensatory tissue to an overload never quite equals the ability of handling the same overload of two normal kidneys. Functional reserve, therefore, should be considered in relation to anatomic conditions to which it is complementary and, when so considered, shows two types:

1. Native: The functional reserve of normal tissue.
   (*a*) Static reserve of function of normal degree in tissue that has undergone no reparatory changes.
   (*b*) Potentially present but inhibited.
   (*c*) Absent in tissue unable to undergo reparatory changes.

30. Hinman, F., and Butler, O. W.: Repair in Hydronephrosis With Reference Particularly to Early and Late Changes After Relief of Brief Obstructions When Opposite Kidney is Not Disturbed, J. A. M. A. **81**:2021-2023 (Dec. 15) 1923.

31. Addis, T., et al., to be published.

2. Acquired: The functional reserve of compensation.
   (*a*) An overadjustmental reserve of function developed in renal tissue that has undergone either partial or complete reparatory changes.
   (*b*) Absent in tissue working to the limit of its ability.

Both the native and acquired types of functional reserve are quite limited and are proportional to the respective types (native and compensatory) of anatomic reserve. There can be no prolonged increase of function without anatomic growth. The margin of functional safety has its foundation in an anatomic reserve.

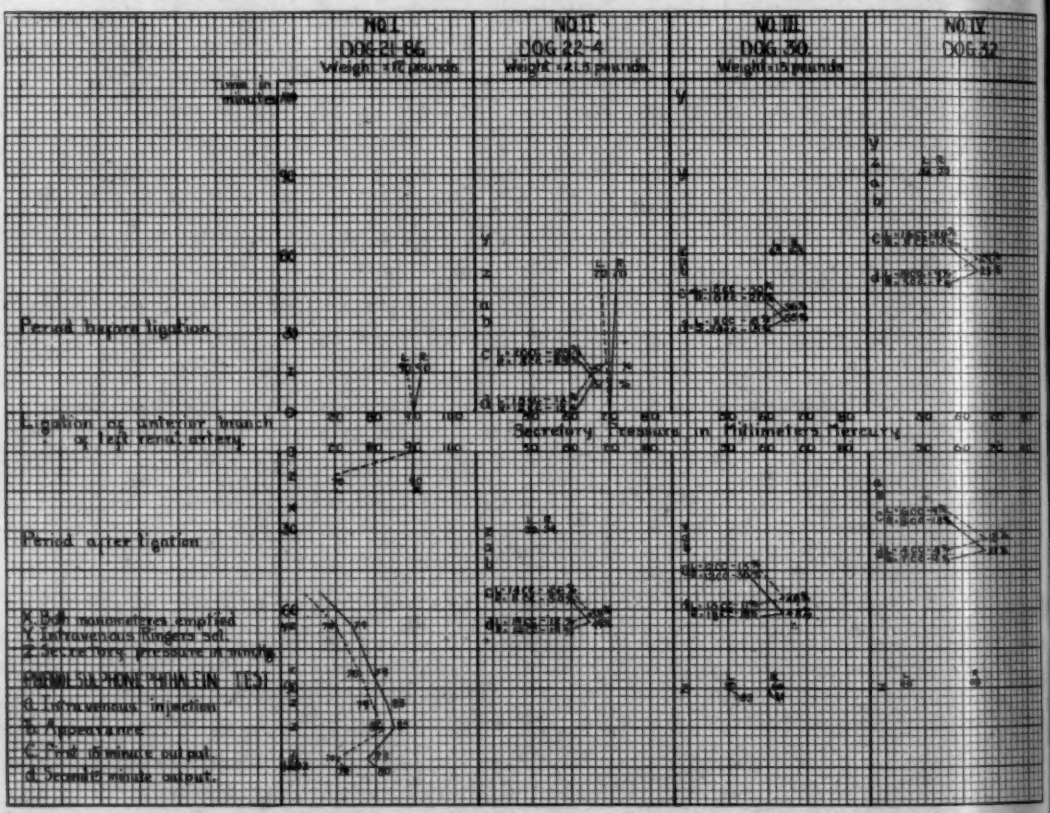

Fig. 2.—Effect of ligation of one branch of renal artery on secretory pressure. In only one of the four experiments was there as great as 30 per cent. difference in the secretory pressure of the two kidneys after ligation of the one branch of the renal artery of one kidney, and in three their difference was only from 15 to 20 per cent., instead of a 50 per cent. reduction, as ordinarily reported, and as might be expected after limitation of blood supply by one-half. Unquestionably, there is not a 50 per cent. anatomic removal. The increased flow and vasa dilatation of the undisturbed half compensate for the loss by ligature, as is also shown by the behavior to phenolsulphonephthalein excretion after ligature; only in Experiment 4 was there a 50 per cent. reduction of phenolsulphonephthalein output, and in this experiment the greatest difference in secretory pressure occurred.

4. SUMMARY OF RENAL RESERVE

Renal reserve power, except for the limited physiologic or static reserve of normal tissue, is potential rather than actual, and refers to the capacity of renal tissue for development. In this sense, it is a reparatory reserve. Irrespective of its divisions into paired structures, a margin of safety is normally provided anatomically in the total mass of renal tissue, just as in the case of the liver, a single structure, or any other organ. The anatomic provision is proportional to the functional demand but is always somewhat in excess of the actual demand, and thus a native anatomic and functional reserve is provided. This static reserve is quite limited, but the reparatory reserve of this same renal tissue may be considerable. It is possible, after removal of two thirds of the total renal mass, for the remnant partly to cover the loss, which it does by growth of the remaining excretory elements. Liver resections are similarly followed by hypertrophy of the liver cells that remain (Rous and Larimore[32]). Removal of one kidney leaves the subject functionally insufficient until the hypertrophic changes of the remaining kidney, in response to the double increase of its activity, have replaced the anatomic loss. Functional reserve, whether static or acquired, and anatomic reserve, native and reparatory, are respectively balanced and coequal, and it is not possible to have an actual functional increase without an anatomic equivalent.

SECTION II. RENAL REPARATORY POWER

Growth in response to an increase of its normal function is common to most organs, both paired and single, and the kidneys form no exception. Lack of one kidney places a double burden of excretion on the other. This renal injury or removal may occur in embryonic, intrauterine or postnatal life, and the consequences of double function on the remaining renal tissue will vary somewhat accordingly. The reparation in the former developmental period is congenital in type and in the latter instance it is distinctly acquired, but in principle both are fundamentally identical.

1. ANATOMIC CONSIDERATION[33]

The kidney forms an interesting study in compensation because of its unique structure and the obscurity surrounding its activity. It will

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32. Rous, P., and Larimore, L. D.: Relation of Portal Blood to Liver Maintenance; Demonstration of Liver Atrophy Conditional on Compensation, J. Exper. Med. **31**:609 (May) 1920.

33. Many facts and illustrations of the following anatomic discussion are taken from a study of renal circulation presented as a scientific exhibit before the Seventy-Third Annual Session of the American Medical Association, St. Louis, May, 1922, and from an experimental study with reference particularly to the mechanism of hydronephrosis presented as part of an exhibit before the Seventy-Fourth Annual Session of the American Medical Association, San Francisco, June, 1923.

be well here to emphasize some of these structural peculiarities. (Consideration of function is given in Part II.)

(*a*) *Renal Tubule.*—The tubule characteristics are well known. It takes origin in an invaginated sphere lined with a flattened and delicate epithelium, Bowman's capsule, the cavity of which is almost obliterated by the glomerular tuft filling it, and opens from it by a narrow neck into the large proximal convoluted tubule, lined with cuboidal cells of varying height. This circles and winds to form a complex coil in the peripheral neighborhood of its capsule of origin, and on its last turn takes a straight course centrically, passes the level of its glomerulus, when it suddenly narrows down to form the descending limb, with a thin pavement-like and peculiar epithelium but a lumen as wide as elsewhere. After a variable and often remarkable length of descent, for the most part through or nearly through the entire medulla, the descending tubule makes a sharp bend and travels back beside its first portion as the ascending limb of Henle's loop. Somewhere near the bend, a sudden transition of the epithelium to an irregular, cubical, short columnar type occurs. The tubule with short columnar epithelium passes peripherally beyond the level of its glomerulus and forms a second coil, the distal convoluted tubule, which intermingles its folds with those of the proximal convoluted tubule and then passes over into the straight collecting tubule. Each tubule is thus seen to have two coils, the one vascular in the glomerulus, and the other a tubular one formed by the proximal and distal convolutions; the latter covers the vascular one like a cap. The four distinct types of epithelium of each tubule have such a remarkably constant regional distribution as to divide it distinctly into four parts: (1) Bowman's capsule; (2) the proximal convoluted portion; (3) the descending limb of Henle's loop, and (4) the ascending limb and distal convoluted portion.

It is well worthy of consideration that the foregoing description of this very specialized structure, except for minor and insignificant variations, is applicable to all higher mammalian kidneys, to the simpler reptilian kidney and even in all its parts to amphibia, the kidney of which does not develop beyond the mesonephric stage (Huber[34]). The adult kidney of man consists of an immense number of these units, about 2,000,000.[35]

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34. Huber, G. C.: The Arteriolae Rectae of the Mammalian Kidney, Am. J. Anat. **6**:391-406, 1906-1907; On the Morphology of the Renal Tubules of Vertebrates, Anat. Record **13**:305-339, 1917.

35. Huschke estimated 2,100,000; Kittelson, 1,040,000, and Sappey, 560,000, in man (Traité d'anatomic descriptive; avec figures intercalées dans le texte, Paris, Masson et Cie, 1850-1864); Schweiger-Seidel, 500,000 in the pig, and Peter, from 200,000 to 300,000, in the cat.

Fig. 3.—Berlin blue injection of a single glomerulus (human kidney) showing several unconnected capillary systems which may show periods of activity or rest independently of each other, and the way that one portion may be injured or destroyed without throwing the glomerulus as a whole out of action.

Fig. 4.—Berlin blue arterial injection, showing the first type of the rich secondary or efferent capillary plexus of the kidney, that in the cortex, which is probably freely anastomotic.

(*b*) *Renal Circulation.*—The manner of blood supply of this extraordinary structure is no less remarkable. All the blood comes in by way of the renal arteries, which carry it by dichotomous branches directly to the capillaries of the glomeruli. There are practically no nutrient blood vessels. What may be taken as the few and insignificant exceptions to this statement, so clearly and simply put by Bowman,[36] in 1842, are as follows: Occasionally, an interlobular vessel is seen to give off a small side twig which breaks up into a plexus of capillaries in the cortex proper without having traversed a glomerulus; an interlobular branch may terminate in the cortex corticis without having traversed a glomerulus, or another may pass completely through the cortex as a perforating capsular artery. A small branch occasionally springs from an interlobar (or arcuate) artery, passing in its course through an atrophic-like glomerulus to terminate in straight vessels in the medulla. The latter are generally regarded as the vestigial vessels to tubular units so low in the cortex as to have had their Henle loops injured and to have atrophied in consequence. Being useless structures, the respective glomeruli also have subsequently atrophied, leaving these vessels as apparent nutrient branches. All the blood, with these four rare exceptions, of no importance physiologically, passes first through glomeruli. The structure of the glomerulus itself has a great significance to physiologic activity. It is not a complex convolution but a series of branches, which may show a double or triple arrangement (Fig. 3). This anatomic fact, together with observations of glomeruli in activity in the frog's kidney, stands in opposition to the idea that when a glomerulus works it always works to its utmost capacity (Part I, Section I). In a double glomerulus, one-half alone may be active and the other half at rest. The capillaries of the glomerulus collect into one or more efferent vessels, which break up into a second capillary network of two general types. The one type of efferent vessels breaks up into a secondary network of capillaries distributed in the cortex on walls of the convoluted tubules and forms their only blood supply (Fig. 4). In the lower zone of the cortex, other efferent vessels from glomeruli abruptly break up to form bundles of branches of uniform size, the arteriolae rectae, which pass down parallel to each other as tufts to supply the lowermost of Henle's loops and the collecting tubules of the medulla (Fig. 5). And this, also, is the only blood supplied to these tubular areas. This unusual circulatory arrangement is well illustrated in Figure 6. Occasionally, the efferent vessels of a glomerulus form both types.

36. Bowman, William: On the Structure and Use of the Malpighian Bodies of the Kidney, with Observations on the Circulation Through that Gland, London, R. and J. E. Taylor, pp. 57-80; reprinted from Phil. Tr. Roy. Soc. London **132**:1842.

From the secondary capillary beds of efferent vessels the blood is collected by veins which in general are of two systems, a superficial, and a deep system conforming in distribution in a very suggestive manner to that of the two types of efferents, cortical and corticomedullary. The superficial set of veins arises from marked umbrella-like or stellate arranged venules in the cortex corticis and cortex, and the deep set from the tuftlike bundles of straight venules, the venulae rectae. The latter parallel the arteriolae rectae and seem to be much more numerous, and the two unite to form an arcuate-like architecture of freely anastomosing vessels in the corticomedullary zone. There is a

Fig. 5.—Berlin blue arterial injection, showing one descending tuft of parallel capillaries from the efferent vessel of a glomerulus, the second type of the secondary capillary system of the kidney, supplying tubular structures of the medulla (Henle's loops).

remarkably free anastomosis between both systems and individual portions of each (Figs. 7 and 8). The venous arrangement of the cat's kidney is peculiarly singular (Fig. 9). In a large series of animals examined (man, monkey, pig, cow, elk, horse, sheep, kangaroo, dog, coyote, deer, rat and mouse), we have not found its like.

There is no anastomosis between arteries: they are distinctly terminal in distribution, and this type of distribution has no parallel in other gland structures. The short course from the aorta direct to glomeruli, the almost complete absence of nutrient vessels, and the double capillary bed, primary in glomeruli and secondary of two types, cortical and medullary, are unique. The arrangement permits an enormous amount of blood to pass quickly through the kidney, an amount

Fig. 6.—Diagram of finer arterial terminations; *A* to *E*, renal capsule and four renal zones; *B*, cortex corticis; *C*, cortex; *D*, corticomedulla, and *E*, medulla; *A* to *H*, the different types of glomerular efferents; *A*, ascending efferent to supply tubule portion in cortex corticis, itself free of glomeruli; *B*, common type of efferent in cortex proper (Figs. 3 and 10); *C*, cortical type and medullary type *(D)* combined; *D*, common type of efferent medullary tufts, the vasa rectae, to supply Henle's loops and the medulla; *E*, the same as *D* except that its glomerulus arises by a solitary direct afferent from the arcuate artery and not from an interlobular branch; *F*, the same as *E* except that the position of the glomerulus is more distinctly medullary; *G*, the same as *F*, except that the afferent is long and the glomerulus diminutive, and *H*, type *G* in which the glomerulus has completely atrophied, giving the appearance of a direct nutrient tuft. From 1 to 7, the types of arterial branching; 1, arcuate artery; 2, 3 and 5, different types of interlobular arteries; 4, a subcapsular or perforating branch; 5, termination in a rare type of direct nutrient to cortex corticis; 6, a young or fresh growth, and 7, a rare direct nutrient to cortex.

unparalleled in other gland structures, even nineteen times as much as the average supply to other organs (Councilman [37]), and an average estimated as six times the amount necessary for its own nutrition. The system, furthermore, is an ideal one for the maintenance of blood pressure. The treelike arrangement of the main vessels, the acute angle at subdivisions, the extraordinarily rapid diminution in diameter as branching proceeds, the smaller caliber of efferent vessels compared

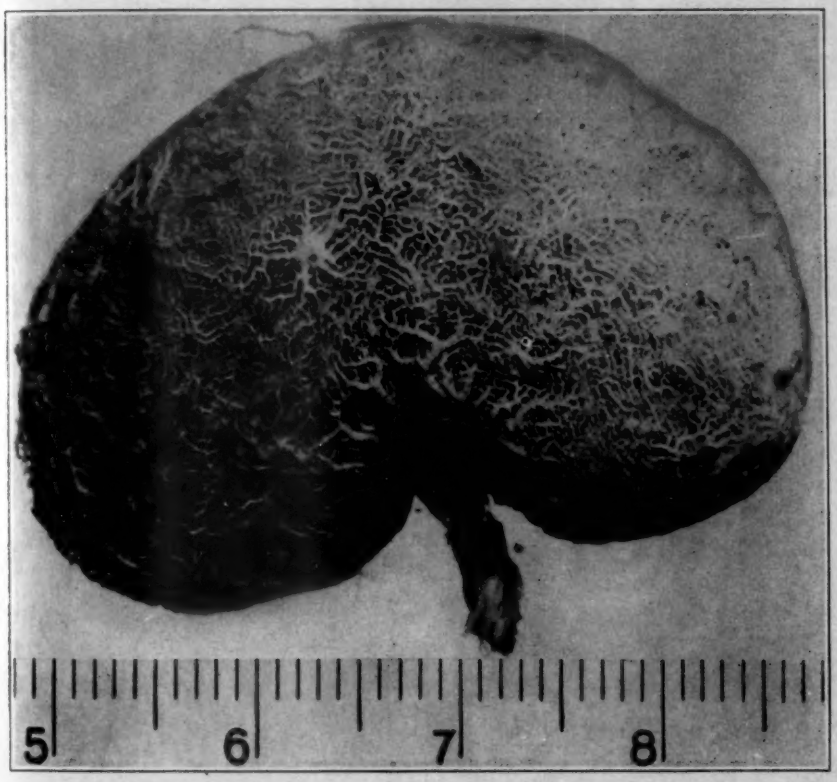

Fig. 7.—Collodion injection of renal venous system (dog) in which maceration and washing has not been completed. The free surface anastomosis is well shown by the stellate starfish-like branching. Comparison should be made with Figure 9 (cat).

to afferent, and the absolute terminal distribution of each branch is a perfect construction for this purpose. A consideration worthy of mention relative to the smaller size of the efferent vessel is that it is called on to carry just that much less fluid away from the glomerulus than is brought to it by the afferent vessel as becomes the tubular filtrate.

37. Councilman, W. T.: The Pathology of the Kidney; Some General Considerations, J. A. M. A. **46**:81-85 (Jan. 13) 1906.

(*c*) *Renal Nerves.*—The nerves of the kidney are mainly, if not wholly, vasomotor, and the splanchnic has long been recognized as the chief vasomotor nerve. The nerve fibers are derived from the semilunar ganglion, with additional small branches from the neighboring plexuses of the suprarenal body and aorta and, occasionally, a direct

Fig. 8.—Collodion injection of venous system of human kidney (pelvis and calices white) in which maceration has been completed. The division into a superficial and deep system of main venous trunks with the free anastomosis in themselves and with each other is clearly seen.

branch from the splanchnic nerve. It is through the semilunar ganglion that vagus communication is effected, although a direct branch of the vagus to the renal plexus has occasionally been noted. From the foregoing source, fibers pass in intimate contact with the entering blood

vessels to the renal hilum where is formed the renal plexus. Ganglion cells have never been found in the renal parenchyma though they occur in large numbers in the renal plexus (Renner[38]). Nerve terminals on afferent and efferent capillaries and venules have been established, and distinct knoblike terminals in glomeruli have been described. The smooth muscle of all the vessels shows typical motor nerve terminations.[39] Terminals supposedly on the walls and between cells of the convoluted tubules and even of Henle's loops led Smirnov to consider them as secretory and sensory, but most physiologists disclaimed any ability to demonstrate secretory fibers, although d'Evant[40] also had previously described similar terminations on the convoluted tubules of such rich supply as to indicate the relative importance of the tubules to function.[41]

(*d*) *Embryology.*—The embryologic development of this singular adult structure has points of significance relative to compensatory changes. According to Huber's[32] complete studies, the bud from the lower end of the wolffian duct gives origin to the ureter, pelvis, calices, papillary ducts and the collecting tubules, while the vital structures of the kidney, the convoluted tubules, Henle's loops and Bowman's capsule, arise from the lower portion of the mesonephric blastema. Glomeruli and their tubular units develop by generations from blastema enveloping Y-shaped ampullae of ureteral branches. A continuation of ureteral branching occurs toward the periphery, forming new ampullae with its cap of blastema, and so on for the successive generations, the youngest of which are always at the periphery. Rienhoff[42] has been unable, in the chick embryo, to confirm this mode of development of the glomerulus. Cultivation by explanting metanephric tissue shows differentiation in situ of the glomerulus from an undifferentiated cellular mass that completely fills the distal end of the convoluted tubule.

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38. Renner, O.: Ueber die Innervation der Niere, Deutsch. Arch. f klin. Med. **110**:101-119, 1913.

39. Smirnov: Anat. Anz. **19**:347, 1901.

40. d'Evant, T.: Compendio di anatomia umana redatto sulla opere piu recenti e secondo l'indirizzo dell'insegnamento ufficiale, ad uso degli studenti in medicina, Naples, D. Cesareo, 1887.

41. For discussion of the literature on the physiology of nervous control of renal activity reference should be made to Renner (Footnote 36); Cushny, A. R.: The Secretion of the Urine, New York, Longmans, Green & Co., 1917, pp. 8-11; Addis (Footnote 5); Marshall, E. K., Jr., and Crane, M. M.: Studies on the Nervous Control of the Kidney in Relation to Diuresis and Urinary Secretion, the Effect of Unilateral Section of the Splanchnic Nerve on Elimination of Certain Substances of the Kidney, Am. J. Physiol. **62**:330 (Oct.) 1922; Hinman and Hepler (Footnote 19).

42. Rienhoff, W. F., Jr.: Development and Growth of the Metanephros or Permanent Kidney in Chick Embryos, Bull. Johns Hopkins Hosp. **33**:392-406 (Nov.) 1922.

Cap formation with subsequent ingrowth of capillaries was never observed. The capillaries also seem to develop in situ from sinusoids which previously had no direct connection with the peripheral circulation.

There are many points needing elucidation in such a tubular and arterial system relative to many details of development. The new capillary anastomoses to the upper pole with atrophy and disappearance of the old blood supply lower down as the kidney ascends, and the enlargement of that capillary bed, most favorably located to become

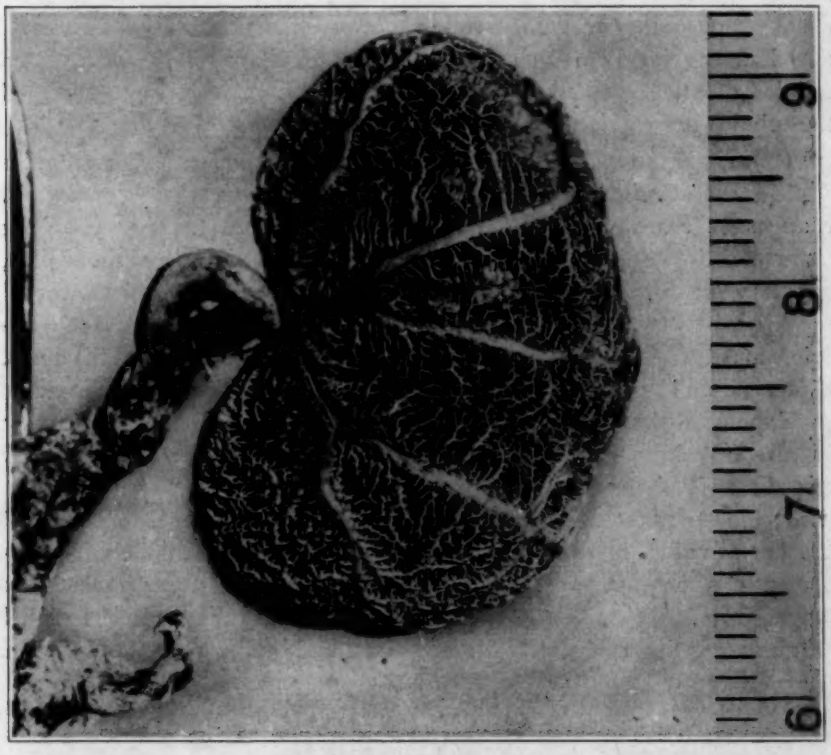

Fig. 9.—Collodion injection of venous system of cat's kidney totally different from dog and man (or any other kidney injected by us). The superficial system is distinctly subcapsular and accounts for many experimental disagreements of this animal with others (text, Richard's experiment) and a difference in eighteen months hydronephrosis (cat, Fig. 15, and dog, Figs. 16 and 17).

a renal artery after the kidney has reached its final position, have been beautifully illustrated by Brödel.[43] But the process is difficult to understand. Figure 9 is the photograph of an arterial celloidin injection of an eight day old fetus. The fetal type of kidney and of its entering

43. Brödel, Max, in Diseases of the Kidneys, Ureters and Bladder, Kelly, H. A., and Burnam, C. F.: New York, D. Appleton & Co., 1914.

arteries is obvious, but in view of these arteries being terminal in character, how is the change to a single renal vessel with anterior and posterior branches effected? Until establishment of renal arteries, the kidney, like the fetus, gets a placental-like nourishment, its sinusoidal circulation being gradually transformed in situ into a capillary circulation as communication with outside vessels is established. The uniformity in persistence of the most direct vascular supply, irrespective of anomalies in parenchymal formation, illustrates the importance of vascularization to function, as well as explains most structural abnormalities. The entering blood vessels seem to take the simplest and most convenient adjustment to the changes in position of the growing parenchyma.

(*e*) *Significance of Structure in Relation to Function.*—The functional significance of the uniform arrangement of this compound tubular structure and its singular blood system is so striking as almost to be obvious and dominates most views of renal activity.[44] Some of the anatomic formations that might be of significance in an understanding of function are: the distinct tubular and glomerular partition, even in the mesonephron of amphibia, the standard quadripartite tubule itself, and the intimate relation of each of its four portions to the similar parts of all other tubules so as to form distinct renal zones; the unique system of blood supply, notably the absence of nutrient vessels, all the blood passing first through glomeruli; the primary "rete mirable," with a single entering and outgoing (usually) vessel, from the latter of which is formed the secondary capillary system to tubules as their only blood supply; the distribution of the secondary capillary bed to the tubules in two ways, one in the zone formed of the convoluted portions, the other in the zone formed largely of Henle's loops; the smaller size of the efferent vessel of a glomerulus, compared to its afferent branch; the more numerous venulae rectae as compared to arteriolae rectae; the distinctly terminal arterial system, but freely anastomosing venous system, and the absence of secretory but rich supply of vasomotor nerves.

Contemplation of them raises many questions. Is each tubule a functional unit? If so, does this unit have an independent and individual blood and nerve supply? All the blood practically passes through the glomeruli but afterward may be sent by way of the secondary capillary network in the outer zone to convoluted tubules or through the straight papillary tufts in the inner medullary zone to Henle's loops. Does it follow, therefore, that some tubules have a special purpose different from others, and portions of the same tubule have activities distinct from other portions?

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44. Discussion of renal function and functional tests is given in Part II, Section I.

The glomerulus extracts from one-twelfth to one-fourteenth of fluid from the blood, leaving a similarly highly concentrated blood to be carried by both types of efferent capillary beds to the respective zones of convoluted tubules and Henle's loops. This degree of fluid extraction is sufficient reason for the smaller size of the efferent branch which may not therefore be altogether for the maintenance of pressure in the glomerulus as is popularly conceived. It would seem impossible, anatomically, for each unit to have an individual system of blood supply as has commonly been illustrated (Fig. 10). The convoluted tubular portion of one glomerular unit may get blood from its own as well as neighboring glomeruli, whereas its own Henle's loop almost

Fig. 10.—Popular conception of efferent blood supply of kidney, which is misleading. The convoluted tubular areas are not wholly supplied by the efferents of their own glomerulus. These portions and Henle's loops, furthermore, get blood from entirely separate sources (Fig. 6). These structural facts have their relation to function. The renal unit is not a tubule but a lobule, the component parts of which cooperate to effect unity of function.

always gets blood from a different glomerulus. As has been shown, some efferent vessels give off both types of secondary capillaries and a concentrated blood from the one glomerulus is then sent to both convoluted and loop portions of the tubule, but this is no proof that it is sent to these portions of its own tubule.

We have no evidence that the concentrated blood from a glomerulus is carried, in the one case, by efferent capillaries to its own individual convoluted portion, or, in the other, to its own loop or, in case of a double efferent capillary network, to its respective convoluted and

loop portions. The concentration and composition both of the blood from a glomerulus and of the fluid taken from the blood by a glomerulus must have considerable influence on the function of the tubule fed by these blood and glomerular filtrates. Anatomically, they often have separate origin, the blood coming from one and the tubular contents from another glomerulus, and it is possible to have tubular contents from one glomerulus, blood to its convoluted tubular portion from another, and to its Henle's loop portion from still a third glomerulus.

The peculiarly rich vascularization for Henle's loops, the predominance in number of venules over arterioles here, as well as their unique and constant structure is difficult to reconcile with any theory of secretory mechanism which regards them as mere drain pipes. If they were this only, Nature would have supplied a simpler system of nutrient vessels than the marvelous bundles of arteriolae and venulae rectae, and avoided such a prodigious loop. The loop varies in length and prominence with species and in some is absent, and the general architecture of the tubule as a whole also varies, but the four types of epithelium corresponding to the four portions of the mammalian tubule are universal. The differences in details of structure of the different portions of the renal tubule for different species are significant of differences of detail in function.

That a free anastomosis exists in the secondary capillary bed formed from efferent glomerular vessels seems certain though we have no direct proof; this mixing of blood supplying tubular elements made possible by such an anastomosis would answer many of the foregoing structural questions regarding tubular units. Such a free capillary anastomosis is indicated by ability to get a back flow through one branch (anterior or posterior) of the renal artery when transfusing the kidney through the other, while it is never possible to get an arterial back flow on injection of the renal vein. Functionally, therefore, the kidney has no structural unit but a group forming a tubular unit in which glomeruli and tubules have distinct and separate duties to perform, but so interdependent as to be practically useless when separated.*

2. CHANGES INCIDENTAL TO RENAL REPAIR

(*a*) *Microscopic Stages of Hypertrophy.*—In view of the foregoing anatomic facts, it is not surprising that the early effect of a double increase of function, as after nephrectomy, overwhelms the circulatory system of the remaining kidney. There is at first an intense congestion. Often the diapedesis and leukocytic infiltration of the interstitial tissues, with swelling of epithelium and dilatation of blood vessels, give a

* Trout, H. F.: The Structural Unit of the Kidney, Embryol. **76**, Publication vs. 332 Carnegie Institute of Washington, 1924.

picture which closely resembles an acute inflammation and the initial changes may be in every way analogous to an acute interstitial nephritis (Albarran [2]). Within seventy-two hours, the epithelium of the tubules swells, and individual cells multiply by mitosis to the point of filling their lumina, and on desquamation often give rise to the formation of cylinders or casts. This acute process shows group distribution in that it does not reach the same severity in all areas. After from four to

Fig. 11.—Microphotograph (high power) of normal rat kidney stained intravitally. The convoluted tubules only take the stain. Comparison should be made with Figure 12, a hypertrophic rat kidney similarly stained and equally magnified.

ten days, the group hyperemia and congestion gradually subside (Morel and Verliac [45]). It is difficult to understand how there can be increased functional activity during this initial stage of growth, and that there is would seem to show the great dependence of renal activity on blood volume, which must be enormously increased.

45. Morel and Verliac: L'hypertrophie renale Compensatrice, Compt. rend. Soc. de biol. **74**:1202-1204, 1913.

With the subsidence of the initial hyperemia, glomeruli and tubules are left in places enormously dilated and fringed often with very large epithelial cells (Golgi,[46] Eckhardt,[47] Rosenstein,[48] von der Stricht,[49] Albarran,[2] Sacerdotti[24]). Karyokinesis of cells is pronounced during the next ten days, so that the epithelium becomes very much hypertrophied and the convoluted portions particularly are enlarged with respect to the thickness of their walls and the size of their lumina. Glomeruli also may grow to be from two to three times their normal volume and are structually perfect (Albarran[2]). This active mitosis and growth is apparently an attempt to repair the acute damage of the first stage and to meet the continued demand of hyperactivity by hypertrophy. As in the earlier change, these hypertrophic appearances first show a group distribution which gradually spreads uniformly throughout the kidney until a final equilibrium of hypertrophy is reached. Hypertrophy is a relative term; a cell may grow slightly or may double or treble its original size, and the size it finally attains is proportional, within certain limits, to the degree and progressive character of the strain to which it is subjected. The complete hypertrophy of the third stage is, therefore, proportional in a way to the demand. In Figure 11 is shown a normal kidney, and in Figure 12 a hydronephrotic repair nodule of a rat of the same size, each similarly stained intravitally. It is seen that considerable cell growth has occurred in the repair nodule which has been subjected, relatively at least, to the greater excretory strain.

(*b*) *Repair by Hypertrophy and by Hyperplasia.*—The question of an actual new formation of glomeruli and tubules has been under debate for many years. Material used for study is so various as to render conclusions difficult of conciliation and has led to a great deal of unnecessary confusion. The remarkable mitosis which is present in areas of parenchymatous and interstitial nephritis has been misinterpreted, many workers believing it a sign of true regeneration. Thus, Lipsky[50] observed new formation of epithelium after inflammation, which Albarran[2] explains as nothing more than connective tissue granulation.

46. Golgi, C.: Neoformazione dell'epitelio dei Canalicoli Orini-Malattia di Bright, Arch. per le sc. med. **8**:105, 1884.

47. Eckhardt, C. T.: Ueber die compensatorische Hypertrophie und das physiologische Wachsthum der Niere, Arch. f. path. Anat. **114**:217-245, 1888.

48. Rosenstein, S.: Ueber complementäre Hypertrophie der Niere, Virchows Arch. f. path. Anat. **53**:141-155, 1871.

49. Von der Stricht, O., cited by Pousson: The Future of the Nephrectomized, Am. J. Urol. **9**:113-132, 1913; Beitrag zur chirurgie der Nephritiden, Berl. klin. Wchnschr. **1**:381-388, 1913.

50. Lipsky: Ueber die Entzundlichen Veränderungen des Epithels der Harnkanälchen, Med. Jahrb., 1872, pp. 155-159.

Simpson [51] studied eighty-one small kidneys of patients from 18 months to 71 years of age, and in five found fairly large sized fields of pure buds. These new tubules are usually lumenless and contain from two to five cells on transverse section. Sprouting of buds from preexisting tubules also was observed. In these kidneys, elongation and widening of the tubules was noted. Very similar observations have been made at the cut border after partial resection or near the margin of infarcts or in areas after chemical injury (Berti [52]). Stoerk [53] had previously

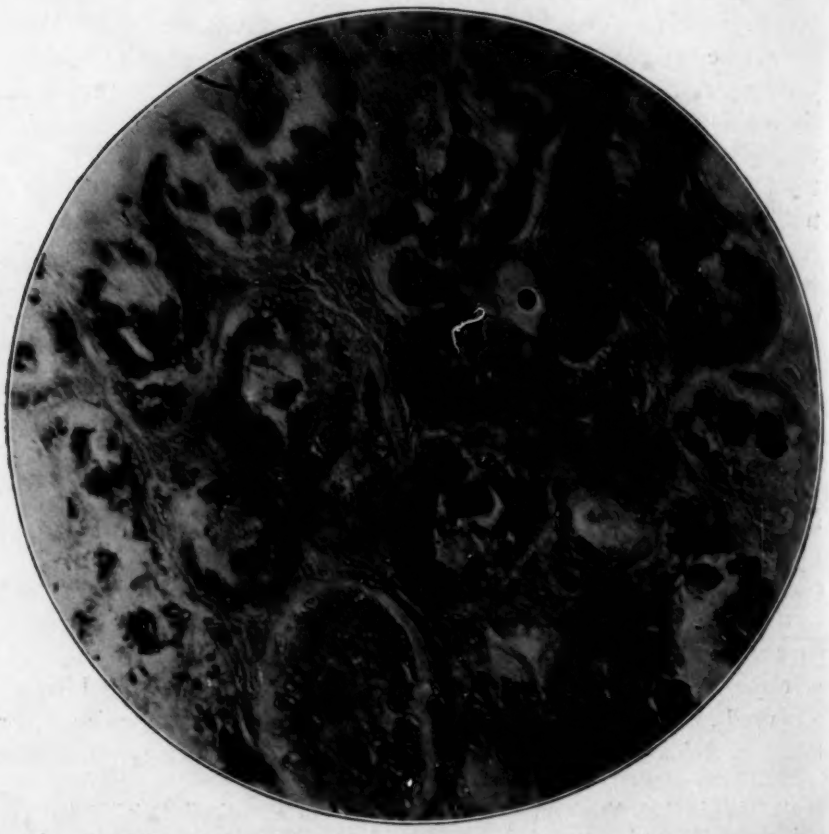

Fig. 12.—Microphotograph (high power) of a hypertrophic repair nodule (middle specimen of Figure 21) stained intravitally, which shows a remarkable hypertrophy as compared to the normal of Figure 11 magnified equally.

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51. Simpson, E. D.: The Small Kidney, with Special Reference to the New Formation of Tubules, J. M. Res. **31**:301-311, 1914-1915.

52. Berti, G.: Experimental Research and Clinical Considerations on Partial Resection of Kidney and Its Compensatory Hypertrophy, Policlinico, Rome, **28**:261-276; 289-309, 1921.

53. Stoerk: Zur Histogenese der Grawitz'schen Nierengeschwülste, Beitr. z. path. Anat. u. z. allg. Path. **43**:393-437, 1908.

described similar conditions in hypernephroma as methods of new formation of renal parenchyma. Before 1900, many observers [54] expressed a belief in true renal regeneration, but, during the same period, evidence in support of a disbelief in it was voiced by a great many more.[55]

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54. Petrone: La Rigenerazione del fegots e del rene per neoformazione dei loro dutti escretorio, Com. preven. Morgagni, 1881, pp. 11-12.

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55. Anzilotti and Fabrini: Contributo sperimentale allo studio anatomopatologico dell' idronefrosi e pionefrosi, Pisa, 1902, p. 56. Aschoff, L.: Regeneration und hypertrophie, Ergebn. d. allg. Path. v. Jahrg., p. 22, 1898. Ballowitz: Ueber Angebornen, einseitigen, Vollkommenen Nierenmangel, Virchows Arch. f. path. Anat. **141**:309, 1895. Barth, A.: Ueber die Histolog, Vorgänge bei der Heilung von Nierenwunden und über die Frage des Wiederersatzes, Arch. f. klin. Chir. **45**:192, 1893.

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Eckardt (Footnote 47).

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Fiori (Footnote 8). Golgi (Footnote 46).

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Lorenz, H.: Untersuchungen u. die Comp. Hypertr. der Nieren, Ztschr. f. klin. Med. **10**:545, 1886.

[Footnote 55 continued on next page]

Since 1900, no one, so far as we know, has stated a belief in true renal hyperplasia except in the case of very young animals.

Reference has already been made to the delay in the full embryonic development of the kidney, even in man up to the sixth year, and, as early as 1882, Ribbert emphasized the significance of this fact when he stated that the compensatory change of an adult organ is effected by hypertrophy but that both hyperplasia and hypertrophy may be active in the case of a young kidney. Eckardt [47] (1888) also clearly presented the differences in compensatory changes as a result of congenital and acquired defects, and recognized the dual character of the changes when the injury occurred in early life. Kittelson [56] (1917) compared the kidney of a new-born infant with that of a 1, 2, 3, 7, 12 and 35 weeks old albino rat, concluding that "the total number of corpuscles in the rat's kidney is apparently reached during the third postnatal week, as but few could be found in process of formation at the age of 2 weeks and none at 3 weeks or thereafter." The natural growth of glomeruli unrelated to an extraordinary demand is referred to later. The conclusion (1902) of Galeotti and Villa-Santa [57] may well be stated in some detail.

The hypertrophy which follows opposite nephrectomy varies markedly according to whether the animal is young and growing or is fully developed at the time of operation.

(*a*) In the former case there is a marked increase in the number of glomeruli, which in general remain normal in size. The convoluted

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Lustig and Galeotti: Trattato di Patologia generale, Ed. 3, Milan, Soc. Ed. Libraria, 1911, p. 726.

Oliver, J.: Histogenesis of Chronic Uranic Nephritis, J. Exper. Med. **21**: 425, 1915; ibid. **23**:301, 1916.

Perl, L.: Anatomische Studien über Compensatorische Nierenhypertrophie, Virchows Arch. f. path. Anat. **56**:305, 1872.

Peruzzi: Sperimentale Arch. de biol. **64**:237, 1910; Ipertrofia ed iperplasia renale compensatoria, ibid. **69**:247-288, 1915.

Galeotti and Villa-Santa (Footnote 57). Neoas. Nauwerck (Footnote 99). Nothnagel (Footnote 58). Podwyssozke (Footnote 112).

Ribbert: Beiträge zur Kompensatorischen Hypertrophie und zur Regeneration, Arch. f. Entwcklngsmechn. d. Organ. **1**:69, 1895.

Rosenstein (Footnote 48). Simon (Footnote 109).

Stoss: Deutsch. Ztschr. f. Thiermed. **12**:284, 1886.

Thorel: Ueber typische und Pseudoregeneration bei Niereninfarkten, Virchows Arch. f. path. Anat. **146**:297, 1896.

Valentin (Footnote 88). Weigert (Footnote 106).

Wolf, M.: Die Nierenresection und ihre Folge, Berlin, A. Hirschwald, 1891.

56. Kittelson, J. A.: Effects of Inanition and Refeeding Upon the Growth of the Kidney of the Albino Rat, Anat. Record **17**:281-297, 1919-1920.

57. Galeotti and Villa-Santa: Ueber die Compensatorische Hypertrophie der Nieren, Beitr. z. Path. Anat. **31**:121-142, 1902.

tubules are increased in number also, but their lumina and the size of the individual cells remain unchanged. The collecting tubules show an increase in the size of their lumina due to the larger number of convoluted tubules ending therein. (*b*) In the latter case, the number of glomeruli and of convoluted tubules is not changed, but there is a marked increase in the size of each.

It may be taken as definitely established, therefore, that regeneration or new formation of any of the secreting radicles of the adult kidney never occurs but that growth of such tissue is always effected by an hpertrophy of its existing elements. But because of the persistence of pseudoglomeruli and embryonic mesonephric blastema well into young adult life, an increase of activity at or before this period occasions growth by the more rapid development of this late generation of glomerulotubular units, and the proportion of hyperplasia to hypertrophy will be relative to the early or late period in embryonic development at which the demand for an increase of function arises.

(*c*) *Relative Variation in the Growth of the Different Renal Structures.*—Increased function of an organ, or part of an organ, can only be caused by an increase of such stimuli as cause its specific activity (Nothnagel[58]). When one kidney is removed, the normal physiologic stimuli to the remaining kidney are doubled, and, if this functional increase causes those elements to enlarge on whichever function is principally dependent, then a study of compensatory hypertrophy should give an indication of the relative importance of the different parts of the renal radicle to total urinary excretion. And a study of the relative degree of hypertrophy of the four portions of the renal tubule in relation to certain specific substances may prove a means of determining the specific function of each portion. It is natural to regard each portion as of some use (as has been discussed). Henle's loop would hardly be so uniformly and peculiarly made if it were a mere duct. "A difference of function is invariably associated with a difference of structure," as Starling[59] has said, which is justification for the inclination to believe that each portion has its own specific responsibility to total function.

In comparative studies of hypertrophy, natural growth must be distinguished from compensatory growth. In the adult there is a fairly uniform proportion of renal mass to body weight for different species, but this ratio is not constant from birth to maturity. According to Kittelson,[56] the more rapid postnatal growth of the medulla occasions this variation, which for practical purposes is so slight as to be negli-

58. Nothnagel: Ueber Anpassungen und Ausgleichungen bei pathologischen Zuständen, Ztschr. f. klin. Med. **11**:82, 1886.

59. Starling, E. H.: Principles of Human Physiology, Philadelphia, Lea and Febiger, Ed. 2, 1915.

gible. But there is a distinct difference in the average size of glomeruli and tubules at birth and at maturity, and this fact is important in a study of the compensatory growth of infancy. Eckardt [47] (1888), for instance, states that the average diameter of the human glomerulus, at birth, is 84.77 microns, while in the adult female it is 195.8 microns, and in the adult male, 213.49 microns. There also is a great difference in the size of glomeruli and tubules of the outer and inner zones of the cortex of the human kidney at birth; according to Kuelz [60] (1899), an average diameter of 99 microns for the former (newer generation at periphery), and 138 microns for the latter. He also found that the glomeruli of the inner zone showed no increase in size up to 2¼ years of age, but during this time those of the outer zone increased to the same average maximum diameter (138 microns) and the average

TABLE 3.—*Glomerular Changes*

	Animal				
	A Young Dog	B Young Dog	1 Young Rabbit	4 Old Rabbit	5 Old Rabbit
Average diameter of glomeruli					
(F) of normal kidney	.....	27.11	19.80	22.60	28.30
(F^1) of hypertrophied kidney	32.66	.....	26.50	43.01	55.14
Average number of glomeruli					
(Z) of normal kidney	...	647	343	540	515
(Z^1) of hypertrophied kidney	979	...	536	591	537
Total infiltration surface of the kidney					
(F × Z) normal	.....	17.540	6.791	12.252	14.514
(F^1 × Z^1) hypertrophied	31,974	.....	14,252	25,413	29.610
$\frac{(F \times Z)}{(F^1 \times Z^1)}$ Ratio of normal to hypertrophied glomerulus	1:1.82	.....	1:2.09	1:2.07	1:2.02

diameter of the adult human glomerulus, as measured by Kuelz, is 238 microns. It is seen that the natural growth of the glomerulus (and tubules), both kidneys being healthy and undisturbed, may be considerable from birth to maturity, and this fact must be considered in a study of compensatory changes following unilateral nephrectomy.

Galleotti and Villa-Santa [57] studied the kidneys of two 4-day old puppies and three rabbits, one young and two fully developed. One pup (A) was nephrectomized (left) and the other (B) used as a control, and both were killed at five months. The left kidney was removed in each of the three rabbits and all (Rabbits 1, 4 and 5) were killed also after five months. Rabbit 1 weighed 490 gm.; the removed left kidney, 3.15 gm. Five months later, when killed, it weighed 1,700 gm., and the compensatory right kidney, 10.85 gm. Rabbit 4 weighed

60. Kuelz, L.: Untersuchungen über das postfetale Wachstum der menschlichen Niere, Inaugural Dissertation, Kiel, 1899.

1,890 gm.; its left kidney, 5.65 gm.; and when killed after five months it weighed 1,900 gm. and its right kidney, 8.25 gm. Rabbit 5 weighed 2,200 gm.; five months later, 2,300 gm.; and its right kidney, 9.57 gm. (weight of left not given). Dog A weighed, at 4 days, 303 gm.; Dog B, 275 gm. The left kidney of Dog A weighed 1.75 gm. When killed after five months, Dog A weighed 3,150 gm.; Dog B, 3,225 gm. Dog A's right kidney weighed 20.05; Dog B's right, 11.69; left, 12.02 gm. The kidneys of all these animals were most carefully studied after being cut and mounted in serial sections 6 microns thick. Accurate, though relative, measurements of the size of the different structures of the normal and hypertrophied kidneys were made after the method of Morpurgo [61] (Zeiss microscope, Oc. 3, Obj. 7 for glomeruli; Obj. 1/12, oil immersion, for tubules, and Abbe's Camera Lucida). The glomerular changes are well shown in Table 3. Irrespective of hypertrophy or

TABLE 4.—*Summary of Convoluted Tubular Measurements*

	Animal				
	A	B	1	4	5
Average epithelial surface area					
In normal kidney	.....	12.70	14.46	15.70	16.52
In hypertrophied kidney	12.88	.....	18.32	22.24	27.20
Average number of nuclei in cross section					
Of normal kidney	.....	7.98	6.86	6.28*	6.84*
Of hypertrophied kidney	8.12	.....	6.81	6.96	6.96
Average size of each cell					
In normal kidney	.....	1.59	2.10	2.46	2.41
In hypertrophied kidney	1.58	.....	2.69	3.19	3.90
Ratio of normal to hypertrophied convoluted tubule	1:1	.....	1:1.26	1:1.41	1:1.64

* The striking feature is the want of variation in the number of nuclei, which would seem to indicate that the increase in the amount of secreting substance is due to an increase in the size of cells rather than to an increase in number. Even in the two adult rabbits (Rabbits 4 and 5), convoluted tubules do not show proportionately as great an increase in size as the glomeruli.

hyperplasia as the method of growth in the adult or young animals, respectively, the filtration surface of every kidney called on to do double duty for five months is about double that of the normal.

If the animal was young in the beginning, growth occurred by an increase in the number of the glomeruli sufficient to double the original surface; if old, by an increase in size which, as seen in Rabbits 4 and 5, is by an actual increase of each glomerulus to twice its original size.

The tubular changes are particularly significant. As natural to expect, those of the convoluted portions are the most marked. Henle's loop and the straight and collecting tubules show none or only slight modifications from the normal, but unfortunately no attempt to measure changes in length is made, and it is probable that growth of this portion of the tubule is mostly by elongation and not by increase in diameter. Table 4 summarizes the convoluted tubular measurements.

61. Morpurgo, B.: Atti. d. Accad. Lincei di Roma **30**:13, 1921.

Addis and co-workers[62] confirm in general these findings of differences in the degree of hypertrophy of the different portions of the renal tubule. They have worked with rabbits that were killed two or three months after nephrectomy, but instead of a 100 per cent. (Galleotti and Villa-Santa [57]) they find only a 22 per cent. increase in size of the glomeruli of the hypertrophied kidney over those of the normal, whereas the proximal convoluted tubules showed an increase of 67 per cent. Even the collecting tubules showed an 8 per cent. increase in size. The average total increase of kidney weight was 66.4 per cent. These relative changes have to be corrected for the average increase of body weight during the two to three months period of compensation, and the average body weight increase was as much as 32.1 per cent.

Such studies as the foregoing seem to show, as is indicated by other methods, that the glomerulus and convoluted tubules are the two structures most actively engaged in urinary excretion. Doubling the normal physiologic stimuli by nephrectomy causes marked growth of both, in young animals mostly by hyperplasia and in the adult solely by hypertrophy. The slight changes noted in the other portions of the tubule, particularly in the loop of Henle, indicate either that these have no active excretory function or, what is more likely, that our present methods have failed to reveal the result of an increase of their activity.

(*d*) *Time Required for Production and Relative Degree of Compensation.*—Consideration of renal reserve emphasizes the relation of structure to function, but, unfortunately, our present inefficient method of study prevents any practical use of a distinction between a functional and an anatomic reserve (Part I, Section I). The one is reparatory in response to an acquired demand of the other, and, theoretically at least, both are relatively proportional. There is no experimental evidence of functional growth without anatomic change accompanying it. The impossibility of a close correlation between tests of renal function and anatomic conditions has led to misinterpretation. Evidence of normal function after renal injury, as given by our known tests, is not proof of an anatomic counterbalance. Functional restoration after renal loss has been discussed above in the consideration of functional reserve, where it is pointed out that there is almost an immediate (from two to three days) functional compensation of the remaining kidney for ordinary work after nephrectomy, but that restoration of function, when estimated by tests which subject renal tissue to an additional strain, is found to be delayed to a period more nearly equal to that required for an anatomic counterbalance. The functional capability of compensatory renal tissue, with the exception of congenital types in which there is

62. This work is unpublished, and I am indebted to Dr. Addis for permission to use it in this connection.

regeneration of tissue, is never quite equal to the capability of normal tissue. Obviously, normal tissue with an unused reserve power for growth is open to greater additional strain than hypertrophic tissue, in which this reserve has been already utilized.

There have been numerous estimations of the time required and the degree of hypertrophy of a compensatory kidney following nephrectomy. Morel and Verliac [45] determined the respective and total weight of the two kidneys in a series of white rats as a control. In another series, they performed left nephrectomy and, after varying periods of from four to fifty days, killed the animal and got the weight of the remaining hypertrophied kidney. In the "first phase," from four to ten days, the kidney increased from 32 to 37 per cent. in weight; in the "second phase," from ten to twenty days, from 9 to 16 per cent., and in the "third phase," from twenty to fifty days, from 11 to 16 per cent. The early greater enlargement they attributed to hyperemia. Paoli Fiori,[22] on the other hand, found that the increase in weight, in guinea-pigs and dogs, describes an ascending curve up to about the twenty-fourth to twenty-sixth day and then remains stationary. In fifty-one animals, for example, the increase of the remaining kidney on the third day was from 3 to 4 per cent.; on the sixth day, from 18 to 20 per cent.; on the eighth to eleventh day, from 30 to 40 per cent.; on the fourteenth to twenty-first day, 50 per cent.; on the twenty-first to thirty-eighth day, not much less than two thirds the total weight of two normal kidneys, and on the thirty-eighth to fifty-first day, no increase over the last (fifth) group. Carnot [63] found the opposite kidney of the rabbit enlarged, on an average of 33 per cent. (from 16 to 53 per cent.), fourteen days after nephrectomy. Tuffier [13] estimated that from twenty to twenty-five days are required for the anatomic completion of a compensatory hypertrophy after nephrectomy, and, in this time, from one fifth to one sixth of the original kidney weight is replaced. It is seen from these figures that there may be considerable variation, which is mostly accountable by failure always to proportion changes in kidney weight to synchronous changes in body weight; nevertheless, a complete replacement by hypertrophy never occurs. Carnot [63] attempted to modify the regular course of such an hypertrophy by physical, chemical and physiologic agents. The roentgen-ray caused, occasionally, a considerable increase (an 88 per cent. increase in five days in one case), the average increase being 50 per cent. Theobromin, lactose and cantharides gave very variable results. Urine in amounts of 20 c.c. per day inhibited the course of hypertrophy (from 0 per cent. to 3.8 and 2.4 per cent.),

63. Carnot, P.: Sur l'hypertrophie compensatrice du rein après nephrectomie unilaterale, Compt. rend. Soc. de biol. **74**:1068-1088, 1913; Sur l'hyperplasie compensatrice du rein après action de divers agents Therapeutiques, ibid. **75**:8-11, 1913.

but extracts of kidney, fetus, thyroid and hypophysis promoted its development (respectively, 33, 39, 55 and 60 per cent. for kidney); from 50 and 53 per cent. for fetus, 32 per cent. for thyroid, and 44, 48 and 61 per cent. for hypophysis). Nigst [64] found that a completed denervation of a kidney failed to influence the usual course of development of hypertrophy in rabbits.

In connection with the weight measurements of hypertrophic rat kidneys, given in the foregoing, the actual measurements of an increase in size are of interest. In Table 5 are shown the average measurements of thirty normal and eighty-nine hypertrophic kidneys of rats of approximately the same age. The cube of these measurements, 1.336, normal; 1.511, at four days; 1.791, at eight days; 1.915, at fourteen days; 1.573, at twenty-eight days; 2.220, at forty-two days, and 2.172, at fifty-six days, shows a gradual increase in size. It is

TABLE 5.—*Measurements of Hypertrophied Right Kidneys, in Rats, After Total Ligation of Left Ureter*

Duration of Hypertrophy	Average Kidney Measurements			Number of Rats Represented	Average Weight of Rats, Gm.
	Length, Cm.	Width, Cm.	Depth, Cm.		
Normal	1.63	0.82	1.00	30	194
4 days	1.63	0.90	1.03	7	210
8 days	1.87	0.93	1.03	10	214
14 days	1.90	0.96	1.05	21	229
28 days	1.90	0.92	1.09	20	243
42 days	1.95	0.99	1.15	17	235
56 days	2.00	0.97	1.12	14	230

seen on examination of sagittal sections of these kidneys that reparatory growth concerns the cortical zone chiefly. These experiments were performed in connection with studies on hydronephrosis and, in many of them, profuse diuresis had existed, and may have had its effect on the hypertrophied kidney though producing no change in the rate of development of hydronephrosis (Hinman and Belt [18]). Considerations of renal mass render of interest the varying periods required for complete hydronephrotic atrophy after total obstruction of the ureter in different species, being relatively short in small animals and prolonged in large ones. The rat requires about ninety days, the rabbit, about 250 days, and the dog, about 500 days, and their weights average 20, 40 and 70 gm. respectively.

The relative growth of medulla and cortex from birth to maturity is of interest in this connection. The change in ratio of kidney weight to body weight with natural growth, already discussed, has been regarded as due to variations in the rate of growth more of the medulla

64. Nigst, P.: Untersuchungen über Kompensatorische und Korrelative Hypertrophie, Schweiz. med. Wchnschr. **51**:155 (Feb. 17) 1921.

than of the cortex, the growth rate of which is more uniform. Thus, at birth (in the rat), the cortex forms 75 per cent of the total, 60 per cent at three weeks, and 74 per cent at maturity (Kittelson [56]); the medulla forms 40 per cent of the kidney at three weeks, but only one-fourth at the other periods. The ratio of medulla to cortex in the adult pig's kidney, which has a relatively large cortex (Peter [65]), is, according to Schweigger-Seidel,[66] 1:8 by weight. In the human kidney, the cortex appears to increase with natural growth relatively much more than the medulla up to 7 years of age, after which both grow equally and double their diameters by the age of puberty (Felix [67]).

There is room for more conclusive experimental work on the question of time required for complete reparatory growth and the degree of growth possible. It is definite that complete anatomic replacement by growth never occurs. After removal of one kidney, anatomic change in its fellow continues for a variable period, the factors governing which need further study. The frequent symptom of renal pain in the remaining kidney for several months after unilateral nephrectomy may be related to these anatomic changes of growth.

3. TYPES OF COMPENSATORY REPAIR

(*a*) *Introduction.*—The congenital and acquired grouping of compensatory change cannot be too closely applied. As already mentioned, hyperplasia is the form of growth of the congenital group, hypertrophy of the acquired; but both an hyperplasia and hypertrophy may occur when the additional burden is placed in the earlier periods of life, evidences of hyperplasia being possible up to as late as the fifth or sixth year, and there is no reason why hypertrophy of renal tissue may not occur in intra-uterine and early fetal life, particularly if, for any reason, the processes of regeneration are slow or defective. In the more definite, acquired group of adult life, three types of change may be recognized: unilateral mass hypertrophy, bilateral mass hypertrophy, and a more distinctly circumscribed or group hypertrophy which may occur on one or both sides.

(*b*) *Congenital Compensatory Hyperplasia.*—When one kidney fails to develop (aplasia, agenesis), or is abnormal from associated defects, or develops imperfectly (hypoplasia) and the opposite renal anlage and developing tissue are normal, the latter compensates for the respec-

65. Peter, Karl: Untersuchungen über Bau und Entwickelung der Niere, Jena, G. Fischer, 1909.

66. Schweigger-Seidel: Die Nieren des Menschen und der Saügetiere in ihren feineren Baue, Halle, 1865.

67. Felix, W.: Die Entwicklung der Harnorgane, Hertwig's Handbuch der vergleich u. experiment Entwicklungsgesch. **3**, 1905.

tive loss. Piersol [68] states that a solitary kidney occurs once in 2,650 cases, which is rather frequent. Sheuer and Sternberg found absence of one kidney seven times in 81,500 cases, and from necropsy statistics (119,055 necropsies), compiled from the literature, found a solitary kidney only once in every 5,953 cases. We find that Meryen, on the other hand, quotes eighty-four cases in 112,459 necropsies, or 1 to every 1,457 cases, and Moore [69] about 1 in 2,400 necropsies. Conditions of absence, atrophy and hypoplasia are pretty apt to be confused, in reporting cases of solitary kidney. In the cases that may be regarded as true solitary types, however, and in which careful measurements have been made, this single kidney has weighed and measured the same as that of two normal kidneys of a similar individual (Rayer,[1] Gruber and Bing [70]). The embryologic compensation of the solitary kidney has been perfect from an anatomic point of view. There is no reason, or proof to the contrary, to believe that a solitary kidney, congenitally come by, is not the equal of two kidneys, both anatomically and functionally. However, the individual with a solitary kidney lacks the renal insurance of a normal person. The usual paired arrangement of the renal mass and the predominance of unilateral injury over bilateral doubles the latter's protection. Disease of a solitary kidney may be sharply circumscribed so that the uninjured portion safeguards function, but the chances of recognition, treatment and repair are obviously diminished by half.

The demonstration of a compensating hypertrophy of the remaining pronephros after removal of its mate in the embryo of *Amblystoma punctatum* (Howland [71]) and failure to demonstrate regeneration or hyperplasia deserves notice in connection with this question of embryonic counterbalance. That the pronephroi are essential to the life of the embryo was proved by death with marked edema resulting after bilateral extirpation. But the interval before the beginning of functional activity of the mesonephros was cared for, after unilateral pronephrectomy, by an hypertrophy of the remaining pronephros in every way analogous to the compensatory hypertrophy of one kidney after nephrectomy in the adult. Both glomeruli persisted after unilateral pronephrectomy (tubular portions on one side alone were removed

68. Piersol, G. A.: Human Anatomy, Philadelphia, J. B. Lippincott Company, Ed. 5, 1916, p. 1887.

69. Moore, F. C.: The "Unsymmetrical" Kidney: Its Compensatory Enlargement, J. Anat. & Physiol. **38**:71, 1903.

70. Gruber, G. B., and Bing, L.: Ueber Nierenmangel, Nierenkleinheit, Nierenvergrösserung und Nierenvermehrung, Ztschr. f. urol. Chir. **8**:259-299 (Sept.) 1921.

71. Howland, Ruth B.: Experiments on the Effect of Removal of the Pronephros of Amblystoma Punctatum, J. Exper. Zool. **32**:355-384, 1921.

at operation) and "since the development of this part of the kidney unit is quite independent of the presence of the tubular portion, its functional activity can be counted on to continue undisturbed. No hypertrophy in glomerular structure, then, would be anticipated nor was such found, for the structural conditions allow free passage of the filtrate ventrally from one side to the other through the celomic cavity. Filtration continues on both sides, the demand for increased physiological activity falling only on the tubule of the unoperated side." The principle of compensation or repair hypertrophy is thus seen to apply even to such a rudimentary organ as the pronephros of an amphibian embryo even in spite of a regenerative power to a high degree. Restitution, in the same sense as follows limb amputation (Harrison,[72] 1918), does not occur, so that regeneration of a kidney is not analogous to the regeneration of a limb, or the lens or gills. It is reparatory in response to a functional demand. The morphologic principle of the marked hypertrophy of the tail of the triton following amputation of the foreleg (Kochs) is different still. It is a correlative hypertrophy. Neither is the congenital hyperplasia, as in solitary kidney, an instance of true regeneration of tissue. There is no actual restitution, and in principle, biologically at least, it is identical with the compensatory hypertrophy of one kidney following opposite nephrectomy, an instance of greater development in embryonic life in response to an increased functional demand.

Infantile kidneys (hypoplasia) occasionally have a pure congenital basis, and in these cases the total renal substance, the opposite kidney having undergone a degree of hyperplasia proportional to the loss from the hypoplasia, is about equal to that of two normal kidneys. A few rare authentic cases (the majority of reports referring to double kidney, horseshoe kidney or to a normally placed suprarenal with ectopic kidney) of multiple or supernumerary kidneys have been reported (Cheyne,[73] Hyrtl,[74] Petrequin, Gérard [75]), and here the total renal substance of the three kidneys is found to be about equal to the normal of two. When these changes of aplasia or hypoplasia occur later in embryonic life, the substitution does not seem to be so perfect, as hypertrophy is now intermingled with hyperplasia. The functional

72. Harrison, R. G.: Experiments on the Development of the Fore Limb of Amblystoma, a Self-Differentiating Equipotential System, J. Exper. Zool. **25:** 413-461, 1918.

73. Cheyne, W.: A Case of Movable Third Kidney, Lancet **1:**215, 1899.

74. Hyrtl, Joseph: Lehrbuch der Anatomie des Menschen, mit Rücksicht auf physiologische Behgründung und praktische Anwendung, Vienna, W. Braumüller, **6:**743, 1851.

75. Gérard, G.: Les anomalies congenitales du rein chez l'homme; essai de classification d'après 527 cas, J. de l'anat. et physiol., Paris, **41:**241; 411, 1905.

limitation of an infantile kidney is of interest in relation to this anatomic discussion. Geraghty and Plaggemeyer [76] found three infantile kidneys among thirty-six cases of renal atrophy in 3,940 necropsies at Johns Hopkins Hospital and emphasized their surgical significance

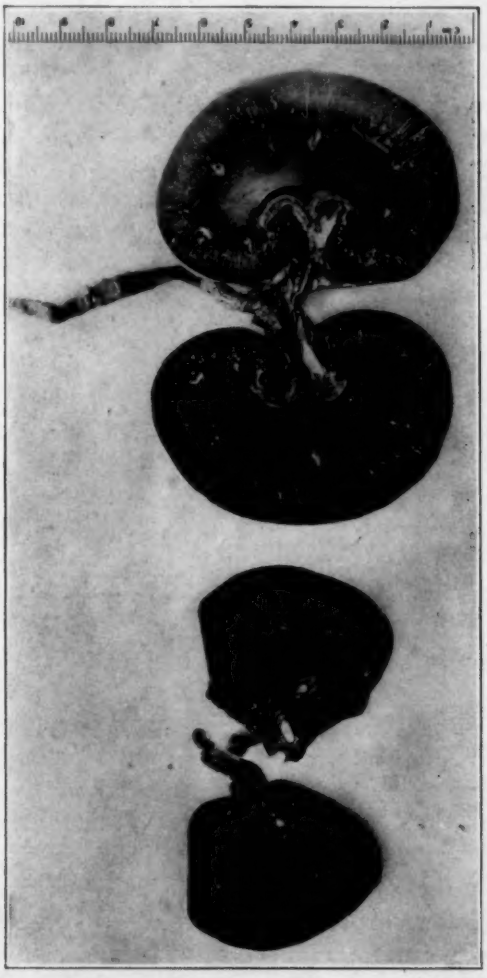

Fig. 13.—Congenital infantile kidney, in which the ureter of the good hypertrophic kidney had been transplanted into the duodenum. The dog died in two weeks and necropsy showed this infantile type of kidney which, without reserve power, was incapable of undergoing hypertrophy and of compensating for the loss of the bigger mate.

76. Geraghty and Plaggemeyer: A Consideration of the Importance and the Diagnosis of the Type of Kidney Known as "Infantile," Tr. Am. A. Gen.-Urin. Surg. **8**:48-70, 1913.

(as will be discussed later). Such tissue has not the ability of growth, is working at its maximum, and succumbs to an overload. In their case, function dropped 80 per cent. with removal of the hyperplastic kidney, weighing 26.4 gm. and at necropsy an infantile kidney, weighing only 6.4 gm. was found (Fig. 13).

A number of curious instances of unilateral hypertrophy of the whole body have come to necropsy. Gardinier [77] finds twenty-eight cases reported up to 1918. In some of these, the kidney of the hypertrophied side has been noted as being much larger than its mate (Hutchinson [78]), but in Gardinier's case no disparity in the size of the kidneys was found. The difference in the size of such kidneys would presumably be due to circulatory conditions and not to compensatory factors.

(*c*) *Acquired Hypertrophy: I. Diffuse or Mass Hypertrophy.* (*1*) *Unilateral Mass Hypertrophy.*—The reparatory changes in a healthy adult kidney as a result of disease, injury or removal of its mate show mass hypertrophy in that they are diffusely distributed. The changes that follow surgical removal have already been described (Part I, Section II). Removal, just as effective but by destruction from disease, does not necessarily give the same compensatory picture in the remaining kidney, although doubling of the amount of work is as surely produced. Albarran [2] has emphasized the inhibition of compensatory hypertrophy in apparently normal kidneys with such diseases as pyonephrosis, tuberculosis and cancer in the opposite side. And this inhibition or failure of hypertrophy in comparison to that following simple uronephrosis or nephrectomy is explained by him as due to the lowered force of reaction of the animal altered by infectious toxins, or to differences in the chemical composition of the blood and particularly to products of disassimilation brought to the kidney for elimination.

In the renal destruction, known as hydronephrotic atrophy, which follows a complete ureteral block, I have found that the hypertrophy of the opposite kidney is perfect in that it is in every way comparable to that which follows experimental nephrectomy. A number of workers, however, have noted biologic changes in the tissues of the remaining kidney after complete ligature of one ureter and, following the lead of Lindemann,[79] have explained them as due to the action of nephrotoxins.

77. Gardinier, H. C.: A Case of Unilateral Hypertrophy of Whole Left Side With Autopsy, Albany M. Ann. **39**:47-57 (Feb.) 1918.

78. Hutchinson: A Case of Semihypertrophy in Which the Internal Organs Were Affected, Brit. J. Child. Dis. **1**:258, 1904.

79. Lindemann: Sur le mode d'Action de certains Poisons renaux, Ann. d. l'Inst. Pasteur **14**:49, 1900.

(*a*) Question of Biologic Changes Due to Nephrotoxins: Lindemann [74] (1900) asserted that he could produce a substance in the serum of guinea-pigs specifically toxic for the kidney of a rabbit by injecting an emulsion of rabbit's kidney into guinea-pigs; that this "nephrotoxin" in the serum of the guinea-pig would not only produce albuminuria but also death by uremia in from three to five days after intravenous injection in the rabbit, and that the rabbit's kidneys presented necrosis of the epithelium of the convoluted tubules resembling that from renal poisons. This finding was confirmed by Nefedieff [80] (1901), Bernard and Meissner,[81] and Castaigne and Rathery [82] (1902), the latter of whom have most vigorously championed the idea. Paoli Fiori [22] (1903) noted a difference in the histologic appearance of the opposite kidney after ureteral ligature as compared to that after nephrectomy, and attributed the more pronounced trophic alterations in the case of ligature to abnormal products in the circulation. Amos [83] (1905) reports the unbelievable finding of death, in rabbits, in every instance after simple ureteral ligature under conditions suggesting uremic coma and attributes death as due "presumably" to the absorption of toxic substances still being secreted by the ligatured kidney. Hirsch and Maschke [84] (1912) allowed a nephrectomized dog to become uremic when its carotid was connected to the jugular of a healthy dog, the kidneys of which as a result showed, on examination, marked changes in their epithelium; but Saccerdotti, in a very similar experiment, obtained quite different results (discussed in the next paragraph, on bilateral hypertrophy). Albarran and Bernard [85] (1903), Pearce [86] (1904) and many others, ourselves included, have not been able to confirm these findings and deny the existence of specific nephrotoxins and cytotoxins. Careful examination of our own specimens of reparatory hypertrophy (more than 400 hypertrophic rat kidneys, and many of pigs, sheep, dogs, cats, rabbits, guinea-

80. Nefedieff: Serum Nephrotoxique, Ann. de l'Inst. Pasteur **15**:17, 1901.

81. Bernard and Meissner, cited by Pousson, A.: The Future of the Nephrectomized, Am. J. Urol. **9**:113-132, 1913; Beitrag zur chirurgie der Nephritidon, Berl. klin. Wchnschr. **1**:381-388, 1913.

82. Castaigne and Rathery: Lesions des reins produites par injection d'emulsion renale ou de serum nephrotoxique, Compt. rend. Soc. de biol. **54**:563-565, 1902; Toxicite de la substance renale et nephrotoxines, Presse mèd., Aug. 13, 1902, pp. 771-775.

83. Amos, B. C.: On the Effect of Ligature of One Ureter, J. Path. & Bacteriol. **10**:265, 1904.

84. Hirsch and Maschke: Experimentelle Untersuchungen über Nephritis, Berl. klin. Wchnschr. **49**:145-147, 1912.

85. Albarran, J., and Bernard: Étude sur les cytotoxines rénales, Arch. d. méd. expér. et d'anat. path., **15**:13, 1903.

86. Pearce: An Experimental Study of Nephrotoxins, Univ. Penn. M. Bull. **16**:217, 1903-1904.

pigs and frogs), developed in consequence of a complete ligation of the ureter of the opposite kidney, shows no changes other than those (congestion, mitosis and growth) that follow nephrectomy when renal poisons of the nature of nephrotoxins are impossible.

(2) *Bilateral Mass Hypertrophy.*—Since the increased functional activity following nephrectomy causes a complementary hypertrophy of the remaining kidney, an experimental or clinical condition which would increase continuously the total renal burden would presumably cause a bilateral hypertrophy. The failure to find evidences of hypertrophy after forced urea feeding has already been referred to (Emge [17]) and leaves one wishing to know if the glomeruli of these urea fed rats also remained unchanged. Carnot [68] reports that urine fed in 20 c.c. amounts inhibits hypertrophy, but the explanation may be as given by Albarran [2] for the inhibition of complementary change with pyonephrosis. Chronic severe diabetes presumably subjects kidneys to a prolonged extra burden of excretion, and many reliable observers (Rayer,[1] Albarran,[2] Saccerdotti [24]) presuppose bilateral hypertrophy in these cases. When it comes, however, to an actual demonstration of bilateral hypertrophy in diabetes, facts are wanting. Futcher,[87] in Osler's Modern Medicine, says that the two kidneys are often found enlarged but does not attribute this to hypertrophy. Curiously, the slight changes that have been noted are degenerative in character and affect Henle's loop only. That the kidneys in diabetes insipidus are also enlarged and congested has often been observed, but the reason for enlargement in both types, as intimated years ago by Valentin [88] and Rosenstein,[48] may be found in a quantitative increase in blood and urinary material in the kidney, and not to actual growth of the epithelial and interstitial structures. Observation of an actual hypertrophy has never been made.

The fundamental interrelationship of function and anatomic conditions has been beautifully demonstrated, however, by such experiments as those of Saccerdotti [24] and Morpurgo.[89]. Saccerdotti produced a very definite bilateral hypertrophy by transfusing the blood of several doubly nephrectomized and uremic dogs into another previously bled but otherwise normal. The hypertrophy of each kidney in this dog was similar to that of a single kidney after opposite nephrectomy. And Morpurgo gives a most striking experimental demonstration of bilateral hypertrophy, in his experiments with lateral celostomy (Siamese lateral

87. Futcher, T. B., in Osler and McCrae: Modern Medicine, Ed. 2, Diabetes Mellitus, **2**:696.

88. Valentin: De Morbis Nervorum cerebralium et nervi sympathici, Bern, 1838.

89. Morpurgo, B.: Sur quelques Relations biologiques entre deux Rats unis par Greffe Siamese, Am. de méd. **8**:1-10 (July) 1920.

grafting). In two rats of equal size and vigor, joined by lateral grafting, he found that after bilateral nephrectomy of one, the kidneys of the other developed an hypertrophy—"aussi forte que celle que, l'on observe chez le rein unique après la néphrectomie unilatérale."

If it were possible in the case of normal kidneys to cause the continuous return into the blood of the products of excretory activity on one side, bilateral hypertrophy should result. Such a condition places a double burden on the undisturbed side as effectually as nephrectomy, and this side will obviously hypertrophy. But the character of the blood supplied to both kidneys is qualitatively the same, and the added stimulus to each will be similar. Therefore, the side whose products are continuously poured back should undergo an hypertrophy equal to that of the side whose products are normally excreted. The six experiments (five dogs, one cat) of Reid,[90] in which he performed ureterovenous anastomosis (into vena cava, left common iliac or jugular) are particularly significant. Dilatation of the transplanted ureter and its pelvis occurred, but there was no back flow of blood up the ureter and no thrombosis or injury of the vein. The bilateral transplantation caused death in from seven to eight days, with symptoms and blood nitrogen findings similar to those that follow bilateral nephrectomy. The uniform occurrence of a hydro-ureter and hydronephrosis and the short duration of the life of the animals destroy the applicability of such an interesting experiment for the study of compensatory hypertrophy.

(*a*) Bilateral Hypertrophy Following Unilateral Ureteroduodenostomy: It is surprising that a conviction of the occurrence of urinary reabsorption from the upper intestinal tract, although unexpressed, should have been so general as to have prevented almost any experimental study of ureteral transplantation into this relatively sterile field. Its many surgical advantages are obvious. Frequent attempts have been made to construct a new bladder from isolated portions of the upper intestine, thus taking advantage of the diminishing number of organisms upward from the rectum. Practically all these attempts have resulted fatally in very brief periods, even in those cases in which the urine drained through the length of the large intestine only, and in spite of good surgical results; and Berg,[91] in reviewing his own and other cases, recognized the significance of intestinal reabsorption. Steinke,[92] in 1909, experimentally performed bilateral uretero-ileostomy

90. Reid, M. R.: Ureterovenous Anastomosis with Observations on Experimental Hydronephrosis and the Blood Nitrogen, Bull. Johns Hopkins Hosp. **29**:55 (March) 1918.

91. Berg, B. N., and Wilensky, A. O.: Drainage in Intra-Abdominal Infection, Ann. Surg. **77**:558-562 (May) 1923.

92. Steinke, C. R.: Transplantation of the Ureters into the Gastro-Intestinal Tract, Univ. Penn. M. Bull. **5**:22, 1909.

in a number of dogs, with fatal results in all, and at necropsy the cause of death remained undetermined. The careful studies of absorption from the ligated intestinal loops in cats by Folin,[93] in collaboration with Denis and with Lyman, give a clear demonstration of the possibility of absorption of the nitrogenous constituents of the urine from the gastro-intestinal tract. Interest in the subject led me, early in 1917, to perform bilateral ureteroduodenal anastomoses and unilateral ureteroduodenal transplantation with opposite nephrectomy on a number of dogs and cats (Table 6). Invariably, these animals died in from seven to ten days, showing tetany and severe diarrhea in their terminal stages. The kidneys in almost all cases appeared surprisingly normal; only occasionally were hydro-ureters and hydronephroses found, giving evidence of a defective transplant and urinary stasis. Analysis at necropsy of the fluid contents of the stomach and duodenum showed urea nitrogen in amounts averaging 200 mg. per hundred cubic centimeters, and a study of the blood nitrogen just before death showed marked accumulation. The following one is typical of such experiments:

PROCTOL

EXPERIMENT 1.—Right ureteroduodenostomy for fifty-nine days. Left nephrectomy. Rise in blood urea nitrogen in eleven days to 485 mg. per hundred cubic centimeters. Death.

Dog 1; an adult, female airedale, weighing 29 pounds (31.3 kg.). Condition excellent.

July 21, 1919, blood urea nitrogen, 14 mg. per hundred cubic centimeters. Phenolsulphonephthalein, 79 per cent. in two hours.

July 23, ether anesthesia; right ureteroduodenostomy by H. P. Smith and A. E. Belt, Fowler-Coffey method.

August 8, recovery had been uneventful. Blood urea nitrogen, 40 mg. per hundred cubic centimeters. Phenolsulphonephthalein, 30 per cent. in two hours.

September 18, blood urea nitrogen, 60 mg. per hundred cubic centimeters. Phenolsulphonephthalein, 70 per cent. in two hours.

A left nephrectomy was done, lumbar route. Left kidney measured, length 5.5 cm., width, 3.2 cm., and depth, 3.2 cm.

September 20, blood urea nitrogen, 72 mg. per hundred cubic centimeters.

September 22, blood urea nitrogen, 190 mg. per hundred cubic centimeters.

September 26, blood urea nitrogen, 252 mg. per hundred cubic centimeters.

September 28, blood urea nitrogen, 340 mg. per hundred cubic centimeters; watery stools.

Constantly drank water; hair sticky, with penetrating odor.

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93. Folin, Denis and Lyman: Protein Metabolism from the Standpoint of Blood and Tissue Analysis, J. Biol. Chem. **11**:87-95, 1912; Origin and Significance of the Ammonia in the Portal Blood, J. Biol. Chem. **11**:161-167, 1912; ibid., **11**:527-536, 1912; Absorption from the Stomach, J. Biol. Chem. **13**:389-391, 1912-1913.

September 29, 8:00 a. m., blood urea nitrogen, 485 mg. per hundred cubic centimeters. Catatonic.

5:15 p. m., pulse 148 per minute; very weak, eyes glassy, hair sticky, penetrating odor. At 8:10 p. m., a slight rose tinge was noted in the liquid stools which were constantly passing; rigor, with a slight, fine tremor. Pulse rapid, growing irregular. Cheyne-Stokes respiration began. The eye reflexes disappear. Death at 8:20 p. m.

Necropsy: Rigor mortis was marked. The heart and lungs were normal; the abdominal contents showed normal sheen; the intestines were in active peristalsis; there were no adhesions. The right ureter ran without interruption into the duodenum; there were no kinks and no dilatations. It was about 4 mm. in diameter. The implanted ureter formed a slight dimple on the mucous surface of the intestine. Very light pressure on the renal pelvis caused a clear amber fluid to flow through this papilla into the lumen of the intestines. There was no leakage, and there were no adhesions about the implanted area. The right kidney was slightly large but normal in appearance. The pelvic capacity was 7 c.c.

Kidney measurements:	Length	Width	Depth	
Right kidney	7.0 cm.	3.8 cm.	3.7 cm.	Removed at necropsy, 9/29/19
Left kidney	5.5 cm.	3.2 cm.	3.2 cm.	Removed at operation, 9/18/19

At about this time (April, 1917) appeared the interesting paper of Baird, Scott and Spencer,[94] with reference to ascending renal infections, but using similar duodenal experiments. Ureteral transplantation was made by drawing the right ureteral end with traction sutures through one of the pancreatic ducts, as had been previously done by Sweet and Stewart[95] (1914, Cases 4 and 40), and then tying these sutures on opposite sides of the intestine. Left nephrectomy later was always followed by death in from seven to twelve days, and at necropsy there were no apparent pathologic lesions to account for it. The ureter was found patent and pouring its contents into the duodenum. The right kidney appeared normal, and the following experiment was done as a test of its continued activity after duodenal transplantation. The dogs were anesthetized before nephrectomy, the abdomen opened and the left ureter identified, isolated, and a catheter inserted into it. Next, the right ureter was cut near its entrance into the duodenum and a catheter inserted into it. During the next forty-five minutes, the right kidney excreted 20 c.c., and the left 15 c.c. The sodium chlorid and nitrogen content of the two specimens was equal. Phenolsulphonephthalein appeared one minute and twenty seconds earlier from the left kidney, but titration showed that the same amount was present in the two specimens.

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94. Baird, J. S.; Scott, R. L., and Spencer, R. D.: Transplantation of Ureters into Intestines, Surg., Gynec. & Obst. **24**:482 (April) 1917.

95. Sweet, J. E., and Stewart: The Ascending Infection of the Kidneys, Surg., Gynec. & Obst. **18**:460-469, 1914.

TABLE 6.—*Experiments with Ureteroduodenostomy*

Serial No.	Animal Experiment	Total Duration of Duodenal Drainage	Uretero-duodenostomy		Ureteral Ligation		Nephrectomy		Ureterostomy		Death		Period from Exclusion of Other Kidney to Death
			Date	Side	Date	Side	Date	Side	Date	Side	Date	Cause	
1	Dog 19-17.....	5 days	2/26/18	Right	9/15/17	Left	.....	.....	12/14/17*	Left	3/ 3/18	Renal insufficiency	.....
2	Cat 17-30.....	17 days	2/19/17	Right	3/ 6/17	Left	.....	.....	.....	.....	3/10/17	Dysentery; pneumonia	4 days
3	Dog 17-66.....	19 days	2/26/18	Right	11/16/17	Left	.....	.....	1/16/18*	Left	3/15/18	Distemper; killed	.....
4	Dog 19-25.....	23 days	9/ 7/19	Right	.....	.....	9/24/19	Left	10/ 1/19†	Right	10/ 6/19	Killed with ether	12 days
5	Dog 17-123.....	25 days	2/20/17	Right	3/13/17	Left	.....	.....	.....	.....	3/19/17	Killed with ether	6 days
6	Dog 17-144.....	26 days	2/23/17	Right	3/13/17	Left	.....	.....	.....	.....	3/23/17	Renal insufficiency	10 days
7	Dog 17-92.....	26 days	3/ 6/17	Right	3/27/17	Left	.....	.....	.....	.....	4/ 2/17	Renal insufficiency	5 days
8	Dog 17-14.....	47 days	10/17/17	Right	.....	.....	11/21/17	Left	.....	.....	12/ 3/17	Killed with ether	12 days
9	Dog 22-16.....	51 days	1/14/22	Right	.....	.....	.....	.....	.....	.....	3/ 7/22	Killed with ether	.....
10	Dog 19-138.....	70 days	7/23/19	Right	.....	.....	9/18/19	Left	.....	.....	9/29/19	Renal insufficiency	11 days
11	Dog 19-139.....	83 days	8/28/19	Right	.....	.....	.....	.....	.....	.....	11/18/19	Killed accidentally; stomach tube in lungs	.....
12	Dog 20-90.....	175 days	3/24/20	Right	.....	.....	9/ 7/20	Left	9/15/20†	.....	9/16/20	Renal insufficiency	9 days
13	Dog 20-89.....	209 days	3/24/20	Right	.....	.....	10/19/20	Left	10/26/20†	.....	10/27/20	Killed with ether	8 days
14	Dog 22-42.....	288 days	3/ 9/22	Right	.....	.....	.....	.....	.....	.....	12/14/22	Killed with ether	.....
15	Dog 21-38.....	381 days	10/28/20	Right	.....	.....	.....	.....	.....	.....	11/14/21	Acute left pyelone-phritis; cystitis	.....
16	Dog 21-37.....	409 days	10/25/20	Right	.....	.....	.....	.....	.....	.....	1/17/22	Killed with ether	.....
17	Dog 21-35.....	443 days	10/22/20	Right	.....	.....	.....	.....	.....	.....	1/ 7/22	Killed with ether	.....

* Ureterostomy to bladder. † Ureterostomy to skin.

Kingo Goto [96] (1918) also performed right ureteroduodenostomy in dogs, with death in from five to ten days after left nephrectomy, but with the astounding assumption that death is due to suspended renal activity, and therefore to renal insufficiency, rather than to intestinal reabsorption. The experiment just cited alone would seem to disprove Goto's conclusion, and several of our own experiments definitely confirm Baird, Scott and Spencer's [94] findings (Table 6, No. 9). The right kidney of Dog 22-16, in spite of its being slightly hydronephrotic, was found to be actively functioning fifty-one days after its ureter had been transplanted into the duodenum.

Further and indisputable evidence of the functional integrity of a kidney whose ureter has been transplanted into the duodenum can be furnished by an experiment in which complete recovery of an animal, with one ureter in the duodenum and the other kidney removed, is found to follow transplantation of the ureter from the duodenum to the skin. In three experiments, we were able to demonstrate the functional integrity of kidneys after ureteroduodenostomy. In Dog 19-25 (Table 6, No. 4), the blood urea nitrogen fell in four hours from 227 mg. per hundred cubic centimeters to 190 mg., in eight hours to 120 mg., and in twenty-four hours to 48 mg. On the third day after skin transplantation blood urea nitrogen was normal, 14 mg. per hundred cubic centimeters, and there was an output of 19 per cent. phenolsulphonephthalein in two hours. In Dog 20-90 (Table 6, No. 12), Protocol 2, the blood urea nitrogen fell from the very high figure of 359 mg. per hundred cubic centimeters to 191 mg. in less than twenty-four hours after implantation to the skin. The ureter had been transplanted to the duodenum for seventeen days in the first case, for 167 days in the second, and for 146 days in the third, and the duration after opposite nephrectomy before implantation into the skin was respectively six, eight and seven days, at which time all three dogs were at the point of death from uremia. The last two experiments particularly are of interest in showing that a kidney which has been useless, for 167 and 146 days, so far as urinary excretion is concerned, has nevertheless been pouring the products of its activity into the duodenum all this time, and when its ureter is brought to a place for actual excretion is found to be functionally competent.

EXPERIMENT 2.—Right ureteroduodenostomy for seventeen days; left nephrectomy. Rise in urea nitrogen to 227 mg. per hundred cubic centimeters in six days. Right ureter removed from duodenum and transplanted to skin. Fall of urea nitrogen to 14.5 mg. per hundred cubic centimeters in three days. Killed.

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96. Goto, Kingo: A Study of Nitrogen Metabolism and of Acidosis After the Transplantation of a Ureter into the Duodenum in Dogs, J. Exper. Med. **27**:449-458 (April) 1918.

Dog 2, a large, brown, adult, male water spaniel, weighing 36 pounds (16.3 kg.).

Sept. 6, 1919, blood urea nitrogen, 10 mg. per hundred cubic centimeters. Phenolsulphonephthalein, 75 per cent in two hours. Weight, 33 pounds (15 kg.).

September 7, right ureteroduodenostomy, Fowler-Coffey method. Weight, 30 pounds (13.6 kg.)

September 10, blood urea nitrogen, 16 mg. per hundred cubic centimeters. Weight, 32.4 pounds (14.7 kg.).

September 14, blood urea nitrogen, 19 mg. per hundred cubic centimeters. Weight, 31.2 pounds (14.2 kg.).

September 24, blood urea nitrogen, 15 mg. per hundred cubic centimeters. Weight, 32.3 pounds (14.6 kg.).

Phenolsulphonephthalein, 30 per cent. in two hours.

Left nephrectomy, lumbar route. Ether narcosis with one-fourth grain (0.016 gm.) of morphin scopolamin.

September 25, blood urea nitrogen, 32 mg. per hundred cubic centimeters. Weight, 30.51 pounds (13.8 kg.)

From this figure, the blood urea nitrogen steadily rose during the next six days.

October 1, 8 a. m., blood urea nitrogen, 227 mg. per hundred cubic centimeters; feces very fluid; over 1 liter collected, which contained 252 mg. urea nitrogen per hundred cubic centimters. The dog was very weak, weighed 29.5 pounds (13.4 kg.), and was catatonic. He was given 250 c.c. of physiologic sodium chlorid solution cutaneously, and, at 9 a. m., the ureter of the right kidney was brought from the duodenum to the skin of the right lumbar region. A short cannula was left in its lumen. Previous to the operation, the animal had been dull and apathetic. Shortly after recovery from the ether anesthesia. he became very much brighter. One hundred and fifty cubic centimeters of urine was the average output per hour for the next six hours. At 10 a. m., blood urea nitrogen, 190 mg. per hundred cubic centimeters. At 4:15 p. m. blood nitrogen, 122 mg. per hundred cubic centimeters. Phenolsulphonephthalein, 21 per cent. in two hours with an appearance time of twenty minutes.

October 2, blood urea nitrogen, 40 mg. per hundred cubic centimeters, and 700 c.c. of urine collected in the last sixteen hours.

October 3, blood urea nitrogen, 31 mg. per hundred cubic centimeters.

October 4, weight, 29 pounds (13.2 kg.). Blood urea nitrogen, 14.5 mg. per hundred cubic centimeters.

Dog in excellent condition but thoroughly wet with urine.

Draining out through lumbar fistula.

October 5, blood urea nitrogen, 17 mg. per hundred cubic centimeters.

October 6, weight, 24 pounds (10.9 kg.) Blood urea nitrogen, 18 mg. per hundred cubic centimeters, and still able to collect from 30 to 50 c.c. of urine per hour. Phenolsulphonephthalein, 19 per cent in two hours. Ureteral opening still draining freely. Killed with ether.

Necropsy: The animal was emaciated and wet, the right ureter draining to the right loin. There were some pus and granulations on the skin surface at this area. The abdomen was smooth and of glistening sheen. The course of the ureter to the skin was tortuous, but no dilatation was noted, and there was no constriction. The pelvic capacity was 10 c.c.. There were no adhesions. The heart and lungs were normal. The duodenal contents were normal; there were formed stools in the rectum. The bladder was small; its wall was greatly thickened, and it was filled with greenish pus, which also filled to dilatation both

ureteral stumps. There was no communication through the ureters with the peritoneum, and no peritonitis was present.

Kidney measurements:	Length	Width	Depth	
Left kidney	6.8 cm.	3.3 cm.	4.0 cm.	Removed at operation, 9/24/19
Right kidney	7.0 cm.	2.7 cm.	3.17 cm.	Removed at necropsy, 10/6/19

Such experiments give indisputable evidence of the continued activity of a kidney whose ureter has been transplanted into the duodenum, and of the predominant, if not complete, reabsorption of the products of this excretion. Since the upper intestinal tract is free of organisms, ascending infections do not occur. A surgically successful transplant will therefore give an ideal experimental condition for bilateral renal hypertrophy. The complete urinary reabsorption nullifies the work of the right kidney as effectively as its removal. The left kidney alone performs actual excretion, does double duty and hypertrophies accordingly. But the blood burden remains the same for the right as the left, and, since there has been no disturbance of its supply and no injury by back pressure or infection to it, the right

TABLE 7.—*Bilateral Hypertrophy*

Dog No.	Duration of Right Ureteroduodenal Transplant	Weight Lbs. Kg.	Right Kidney Length, Cm.	Right Kidney Width, Cm.	Right Kidney Depth, Cm	Left Kidney Length, Cm.	Left Kidney Width, Cm.	Left Kidney Depth, Cm.
138.....	59 days	29 (13.2)	7.0	3.8	3.7 (98)*	5.5	3.2	3.2 (56)
19-25.....	17 days	24 (10.9)	6.8	3.3	4.0 (89)	7.0	2.7	3.1 (58)
20-89.....	217 days	17 (7.7)	5.4	2.6	2.5 (35)	4.6	1.9	2.7 (23)
139..... (Protocol 3)	83 days	19 (8.6)	5.5	2.7	2.6 (38)	5.0	2.6	2.7 (35)

* Numbers in parenthesis signify cubic measurement, length by width by depth.

kidney should react to this double functional load by a similar hypertrophy. A careful study of the kidneys in these experiments bears out this assumption. In two (Dogs 22-16 and 20-89), the right kidney was slightly hydronephrotic. In the other four cases, of fifty-nine, seventeen, 146 and eighty-three days after ureteroduodenostomy, respectively, the right kidney, though not hydronephrotic, was as large or larger than the left, as is shown in Table 7.

The following protocol in which simple ureteroduodenostomy alone was performed and the dog killed in eighty-three days is typical in showing that both kidneys have undergone an equal hypertrophy.

EXPERIMENT 3.—Bilateral renal hypertrophy. Right ureteroduodenostomy. Killed in eighty-three days.

Dog 3, a female, adult, black spaniel, weighing 19.1 pounds (8.6 kg.).

July 21, 1919, blood urea nitrogen, 15 mg. per hundred cubic centimeters. Phenolsulphonephthalein, 76 per cent. in two hours.

July 22 to August 28, blood urea nitrogen ranged from 15 mg. per hundred cubic centimeters to 13.5 mg. per hundred cubic centimeters in five determinations.

August 28, right ureteroduodenostomy; ether anesthesia.

September 8, blood urea nitrogen 19 mg. per hundred cubic centimeters. Phenolsulphonephthalein, 75 per cent. in two hours.

November 18, killed accidentally by stomach tube in lungs.

Necropsy: The lungs were filled with frothy, watery fluid; there were many adhesions in the abdomen about the site of transplantation. The right kidney showed no hydronephrosis, and there was no hydroureter. The left kidney was equal in size (Fig. 14).

Kidney measurements:	Length	Width	Depth	
Right kidney	5.5 cm.	2.7 cm.	2.6 cm.	Removed at necropsy, 11/18/19
Left kidney	5.0 cm.	2.6 cm.	2.7 cm.	Removed at necropsy, 11/18/19

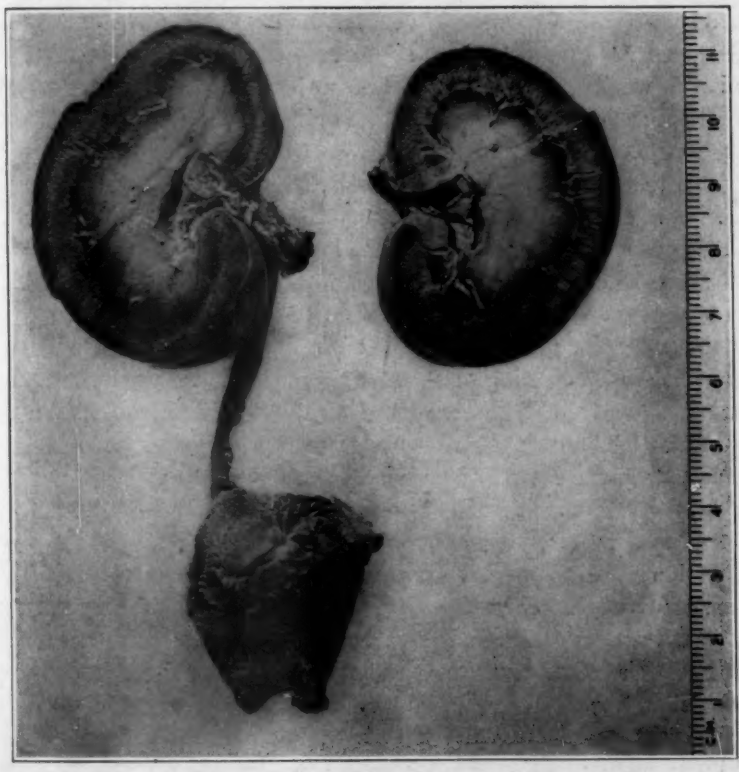

Fig. 14.—Bilateral renal hypertrophy in Dog 19-139; the ureter had been transplanted into the duodenum from Aug. 28 to Nov. 18, 1919, a period of eighty-three days (text). The condition of the transplanted kidney is perfectly healthy. There is no infection, no back pressure changes and, microscopically, as well as grossly, it has undergone as marked hypertrophy as the undisturbed kidney which had been doing all the actual renal work for eighty-three days.

We shall have occasion to refer back to these experiments of bilateral hypertrophy in discussing conditions of renal atrophy and wish to emphasize this fact, that infection is absent in these hypertrophic kidneys; also that the renal parenchyma appears normal, except for the evidences of hypertrophy, that it is still functionally active.

and that there is no tubular dilatation or evidence of ureteral obstruction.

II. *Circumscribed or Group Hypertrophy.*—(*a*) Introduction: Injury to renal tissue, with the very few exceptions of diffuse lesions, shows, particularly in the early stages, a group distribution and as the lesion spreads, there is a distinct variation in the severity of involvement of different areas, less injured portions being intermingled with those of more advanced injury. The destructive processes from bacterial or chemical toxins, whether bilateral or unilateral, do not affect the whole parenchyma simultaneously, and the inequality of functional work performed by less injured as compared to more injured areas probably causes an exaggeration of the initial difference because of the natural tendency of the less injured areas to undergo hypertrophy. Trauma, tumor, infarction, infectious or toxic nephritis, stones and retention may all distribute their destructive action unevenly in the different renal lobes of the same kidney. With group injury there is group compensation in the individual renal mass similar in principle to the hypertrophy of a normal kidney with loss of function of its mate. Doubtless the increased functional activity brings a better blood supply, better nourishment and greater resistance to that portion capable of response while the part incapable suffers proportionately. Group distribution of areas of greater and less injury is promoted by the factor of activity versus inactivity. The unaffected areas may show considerable hypertrophy in an attempt to take the place of those parts which succumb.

The literature abounds with references to this type of injury dispersion. In studying chemical nephritis, many investigators have found that all parts of the kidney do not participate to the same degree, and that, after a time, compensatory hypertrophy of the more healthy parts occurs (Chauffard,[97] Golgi,[98] Nauwerck[99]). Charcot and Gombault[100] describe islands of injury and islands of hypertrophy in nephritis, and many histologic studies of small granular kidneys (Küster,[101], Weber,[102]

97. Chauffard, A.: Des hypertrophies renales compensatrices au cors des nephrites chroniques, Semaine méd. **18**:505-507, 1898.

98. Golgi, C.: Sulla ipertrofia compensatoria dei reni, Arch. per le sc. med. **6**:3, 1883; Sur l'hypertrophie Compensative des reins, Arch. ital. de biol. **2**:268-273, 1882-1883.

99. Nauwerck: Beiträge zur Kenntniss des Morbus Brightii, Beitr. z. path. Anat. u. z. allg. Path. **1**:1, 1886.

100. Charcot and Gombault: Progr. Med., 1878, p. 82.

101. Küster, E.: Die Chirurgischen Krankheiten der Nieren, Deutsch. Ztschr. f. Chir. **1**:163, 1896.

102. Weber, F. P.: Compensating Hypertrophy of Renal Secreting Tubules in Cases of Granular Contracted Kidneys, Practitioner **99**:260 (Sept.) 1917.

Ziegler [103]), of interstitial nephritis (Fortlage,[104] Golgi,[98] Ribbert,[105] Weigert [106]) and of parenchymatous nephritis (Golgi,[98] Albarran [2]) point to a definite attempt to shunt the renal function to a small, less injured portion of the renal parenchyma. Thorel and Litten [107] describe compensatory hypertrophy of uninjured renal tissue in the neighborhood of renal infarcts, which Albarran finds in every way analogous to that seen in partial resection (described in detail by Maas,[108] Simon,[109] Tillmanns,[110] Pisenti [111] and Podwyssozki [112]). Ribbert noted in the kidney of a syphilitic infant areas atrophied by interstitial nephritis alongside of areas showing compensatory hypertrophy. The literature of the later nineteenth century is full of such observations of histologic changes of growth with all sorts of renal disease and injury both clinical and experimental, and which were occasion for a spirited dispute on the part of cellular pathologists as to these changes being evidence merely of hypertrophy or often of true new formaiton—hyperplasia.

(*b*) In Experimental Repair Hydronephrosis: A study of the repair that follows relief of ureteral obstruction is of particular interest in relation to this type of hypertrophy in renal compensation. Hydronephrotic atrophy, as has been stated, is a definite type of group degeneration, progressing most extensively at first in the lateral portions, next in the polar areas, and, lastly, in the median sagittal parts. A study of the relation of weight to pelvic contents at different periods

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103. Ziegler: Special Pathological Anatomy, Ed. 9, pp. 773-774.

104. Fortlage: Ueber die compensatorische, der Glomeruli bei Nephritis Interstitialis (Hypertrophie), Dissertation, Bonn, 1884.

105. Ribbert: Compensatorische Hypertrophie der Harnkanälschen bei nephritis interstitialis, Sitzungsb. d. Niederrh. Gesellsch. f. Natür. u. Heilkunde, June, 1881.

106. Weigert, C.: Die Bright'sche Nierenkrankung vom Pathologisch-Anatomischen standpunkte, Samml. klin. Vortr., 1879, pp. 1411-1460.

107. Thorel and Litten: Untersuchungen über den hämorrhagischen infarct und über die Einwirkung arterieller Anämie auf das lebende Gewebe, Berlin, A. Hirschwald, 1879.

108. Maas, H.: Klinische und experimentelle untersuchungen über die subcutanen Quetschungen und Zerreissungen der Nieren, Deutsch. Ztschr. f. Chir. **10**:126-172, 1878.

109. Simon, G.: Chirurgie der Nieren, Erlangen, **10**:82, 1871-1876.

110. Tillmanns, H. (Footnote 49); cited by Pousson: Experimentelle und anatomische Untersuchungen über Wunden der Leber und Niere, Ein Beitrag zur Lehre von der antiseptischen Wundheilung, Virchows Arch. f. path. Anat. **78**:437-474, 1879.

111. Pisenti: Sur la cicatrisation blessures du rein et sur la regeneration partielle de cet organe, Arch. ital. de biol. **6**:1884.

112. Podwyssozki, W.: Experimentelle Untersuchungen über die Regeneration der Drusengewebe, Beitr. z. path. Anat. u. z. allg. Path. **1**:259, 1886.

of ureteral obstruction shows a remarkable gain in tissue mass in the early periods, explainable on the basis only of group changes (Fig. 14). Relief of obstruction, in the course of any of these progressive periods, will be expected to have a corresponding different degree of repair, but this expectation is found to be fulfilled relatively, and for early periods of repair only. There is reason to believe that a kidney with a complete ureteral block continues to show some degree of aborted activity up to the point of complete hydronephrotic atrophy; otherwise, the formation of large hydronephrotic sacs would not occur. The anatomic evidence of repair which follows removal of an obstruction of as long even as sixty days is good experimental proof of the continuation of such activity.

The experimental investigation of the degree of recovery of a hydronephrotic kidney after the obstruction causing it has been removed has not been extensive,[113] and falls into two groups. In one the opposite healthy and compensatory kidney has been removed either at or some time after the removal of the ureteral obstruction; in the other, the opposite and healthy kidney has not been disturbed in the course of the repair experiment. In the experiments with opposite nephrectomy, the complete burden of total renal work has been suddenly thrown on the injured repair side, thus overwhelming a previously functionless organ. In the experiments that leave the opposite kidney undisturbed, the hypertrophy which has occurred on the healthy, undisturbed side in compensation for the increased burden must have a considerable influence on the degree of repair of the injured side after removal of its obstruction by lessening the stimulus to repair. If the compensatory side is fully capable, there is less or little reason for repair on the injured side.

In Table 8 is given a summary of the actual experiments we have found reported that have been performed for the purpose of testing repair after hydronephrosis. The results do not offer very much encouragement to the conservative surgeon. However, they are mostly short time experiments and, therefore, are not a complete test of anatomic possibilities. Donati[114] belittles the usefulness of the con-

113. For discussion and literature, reference should be made to the articles on experimental hydronephrosis by me and my co-workers.

Hinman, F.: Experimental Hydronephrosis, Repair Following Ureterocystoneostomy in White Rats with Complete Ureteral Obstruction, Tr. Sect. Genito-Urin. Dis. A. M. A. **69**:117, 1918.

114. Donati, M.: Ricerche sperimentali sul valore del trattamento conservativo dell'idronefrosi, Gior. d. r. Accad. di med. di Torino **4**:597-612, 1904. Contributo sperimentale allo studio dell'anatomia, fisiopatologia e trattamento dell'idronefrosi, Clin. chir., Milano, **15**:191, 273, 1907.

servative treatment of hydronephrosis. Johnson [115] found, in two experiments, that rabbit kidneys obstructed for two weeks might regain, except for varying amounts of atrophy in their lateral portions, sufficient normal structure to compensate for the loss of their opposite healthy partner, but it took forty days for a functional compensation of a seven day hydronephrosis, and 152 days, of a fourteen day hydronephrosis. Rautenberg's [116] conclusions are particularly worthy of emphasis in view of our own different interpretation of his results. His eighteen experiments, he believes, show that repair hydronephrotic parenchyma is not viable and that the injury of even a fourteen days' obstruction is that of a true, progressive, toxic degeneration with ultimate destruction, similar to nephritis.

Our own experimental results in these two groups of repair experiments will be briefly presented at this point, as they conform closely to those reported by others for these two groups, but, in order properly to recognize the several conditions of repair, the complete series of experiments will be divided into four groups in place of two, the third group being dealt with in the division on atrophy (Part I, Section III), and the fourth group in the division on counterbalance (Part I, Section IV). In order to avoid confusion, the four groups of experiments are given below, and should be considered as a unit in relation to the major problem of counterbalance, although each group has its fractional and particular significance.

Group 1: Hydronephrotic repair after ureterocystoneostomy and opposite nephrectomy.

Group II: The condition of repair in the early period after ureterocystoneostomy when the opposite kidney is healthy and undisturbed.

Group III: The condition of repair in the late period after ureterocystoneostomy when the opposite kidney is healthy and undisturbed.

Group IV: Hydronephrotic repair after ureterocystoneostomy when the opposite kidney itself is gradually destroyed by hydronephrotic atrophy from partial obstruction of its ureter.

1. Group I of Repair Hydronephrosis: Ureterocystoneostomy after hydronephrosis with opposite nephrectomy. The changes in early hydronephrosis from complete ureteral obstruction show many points of interest relative to structure and repair. A continuation of renal activity, in spite of the block to the outlet by way of the ureter, is absolutely necessary for the production of pelvic dilatation. Otherwise, primary atrophy occurs. We have shown the probability of

115. Johnson, R. A.: Renal Function in Experimental Hydronephrosis, J. Exper. Med. **28**:193-212 (Aug.) 1918.

116. Rautenberg, E.: Die Folgen des zeitweiligen Ureterverschlusses, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **16**:431-475, 1906.

TABLE 8.—*Reported Studies of Repair Hydronephrosis*

Name of Experimenter	Animal Used	Duration of Complete Ureteral Obstruction	Ureteral Transplantation to	Group I: Opposite Kidney Undisturbed	Group II: Cases of Survival on Repair Kidney after Opposite Nephrectomy			Result	Remarks
					Nephrectomy	Ureteral Ligation	Subsequent Period		
Donati	13 rabbits; 2 dogs	From 10 to 100 days	Bladder	(In 11, removed a fragment from kidney for comparison with late result)	.....	.....	.....	.....	
Amas	Rabbit	14 days	Skin	35 days	.....	.....	.....	Killed	Opposite kidney showed no change
Boetzel	Rabbits	21 days	Bladder	15 hours	.....	.....	.....	Killed	Studied excretion of toluidin blue; repair of ability to excrete it after obstruction up to from 20 to 30 days
		21 days	.....	15 hours	.....	.....	.....	Killed	
		22 days	.....	17 hours	.....	.....	.....	Killed	
		22 days	.....	24 hours	.....	.....	.....	Killed	
		27 days	.....	48 hours	.....	.....	.....	Killed	
		31 days	.....	68 hours	.....	.....	.....	Killed	
		40 days	.....	68 hours	.....	.....	.....	Killed	
Hinman	White rats	14 days	Bladder	146 days	.....	.....	.....	Killed	Studied reaction to intravital stain, diamin blue, and anatomic changes of repair; convoluted tubules stained intravitally up to 60 days obstruction and formed repair nodules up to this time
		60 days	Bladder	119 days	.....	.....	.....	Killed	
		60 days	Bladder	165 days	.....	.....	.....	Killed	
		95 days	Bladder	99 days	.....	.....	.....	Killed	
		120 days	Bladder	116 days	.....	.....	.....	Killed	
		120 days	Bladder	92 days	.....	.....	.....	Killed	
Routenberg	Rabbits	21 days	Bladder	24 days	.....	.....	.....	Killed	
		42 days	Bladder	34 days	.....	.....	.....	Killed	
		42 days	Bladder	70 days	.....	.....	.....	Killed	
		45 days	Bladder	86 days	.....	.....	.....	Killed	
Bradford	Rabbits	11 to 40 days	Bladder	7 to 50 days	.....	.....	.....	Killed	
Elderlein	Dog	After some time	Bladder	At various periods	.....	.....	.....	Killed	Quoted by Rautenberg
Latchem	Dog	14 days	Bladder	311 days	.....	.....	.....	Killed	Good preservation of kidney
	Dog	14 days	Bladder	316 days	.....	.....	.....	Killed	

Corbett.....	Rabbits	24 hours	Bladder	.....	8 days	.....	Not stated	.....	
		6 days	Bladder	.....	7 days	.....		.....	
		22 days*	Bladder	.....	Same time as	.....	37 days	Killed	
		23 days*	Bladder	.....	ligature removed	.....	55 days	Killed	
Fiori	Rabbit	28 days	Bladder	.....	.....	At same time	26 hours	Died	
	Rabbit	90 days	Bladder	.....	.....		7 days	Died	
	Dog	160 days	Bladder	.....	.....	10 days	9 days	Died	
Rautenberg.....	Rabbits	14 days*	Bladder	.....	9 days	.....	49 days	.....	Living
		15 days	Bladder	.....	19 days	.....	9 days	Died	
		16 days	Bladder	.....	15 days	....	49 days	Died	
		21 days	Bladder	.....	11 days	.....	5 days	Died	
		21 days	Bladder	.....	23 days	.....	26 weeks	Died	
		21 days*	Bladder	.....	22 days	.....	1 year	Died	
		21 days	Bladder	.....	28 days	.....	3 days	.....	
		22 days*	Bladder	.....	31 days	.....	1 year	.....	Living; concluded that hydronephrosis is a progressive toxic degeneration little influenced by repair procedures
		28 days	Bladder	.....	24 days	.....	2 days	Died	
		29 days	Bladder	.....	16 days	.....	2 days	Died	
		42 days	Bladder	.....	155 days	.....	4 days	Died	
		42 days	Bladder	.....	.....	74 days	4 days	Died	
		42 days	Bladder	.....	.....	74 days	4 days	Died	
		42 days	Bladder	.....	117 days	.....	4 days	Died	
Donati.....	Rabbit	10 days	Bladder	.....	.....	15 days	16 days	Died	
	Rabbit	14 days	Bladder	.....	.....	16 days	3 days	Died	
	Rabbit	.....†	Bladder	.....	.....	.....	6 days	Died	
	Rabbit	.....†	Bladder	.....	.....	.....	4 days	Died	
	Rabbit	24 days	Bladder	.....	35 days	.....	4 days	Died	
	Rabbit	40 days	Bladder	.....	15 days	.....	3 days	Died	
	Dog	70 days	Bladder	.....	136 days	.....	24 hours	Died	
	Dog	80 days	Bladder	.....	160 days	.....	2½ days	Died	
Johnson.....	Rabbit	3 days	Bladder	.....	5 days	.....	23 days	Died	Phenolsulphonephthalein excretion did not reach normal until 40 days in 7 day, and 152 days in 14 day obstruction
		7 days*	Bladder	.....	16 days	.....	40 days	Killed	
		14 days*	Bladder	.....	35 days	.....	152 days	Killed	
		17 days	Bladder	.....	14 days	.....	9 days	Died	
		19 days	Bladder	.....	3 days	.....	4 days	Died	
		19 days	Bladder	.....	18 days	.....	3 days	Died	
		21 days	Bladder	.....	11 days	.....	6 days	Died	

* Living on repair kidney after opposite nephrectomy.
† One half of kidney resected.

pyelovenous back flow (Hinman and Lee-Brown [117]) being the basis of continued urinary secretion, and in Figure 15 is shown the remarkable increase of renal mass independent of sac contents occurring in successive stages of hydronephrosis, in rabbits, and largely due to attempts at group hypertrophy obviously impossible without renal activity. Confirmation of the findings of others, that a hydronephrotic kidney of fourteen days or less duration is able to perform total func-

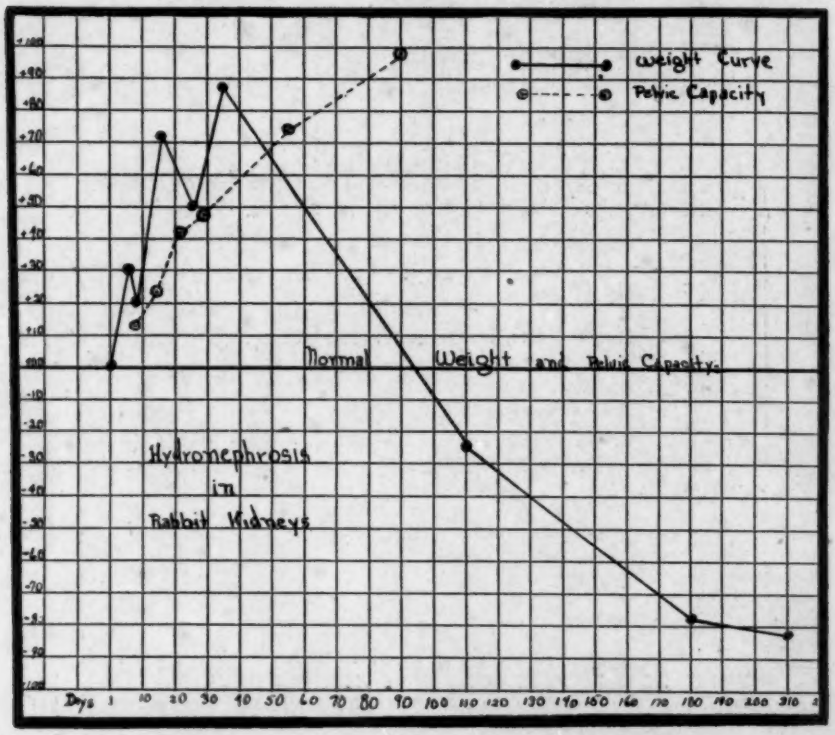
Weight Curve
Pelvic Capacity
Normal Weight and Pelvic Capacity.
Hydronephrosis in Rabbit Kidneys
Days 1 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210

Fig. 15.—Variation in weight of adult rabbit kidneys during the successive stages of hydronephrosis, independent of the accumulated fluid contents. The primary gain has been attributed to group hypertrophy, inflammatory infiltration, and laying down of connective tissue.

tion when required to do so by the removal of its hypertrophic mate is given by several such experiments by us, in cats, of which Experiment 4 is an example.

Experiment 4.—Left ureteral obstruction for twelve days; left ureterocystoneostomy, and, after ten days, the right kidney removed. The cat lived in good health for another 110 days, when it was killed.

117. Hinman, F., and Lee-Brown, R. K.: Pyelovenous Back Flow, Its Relation to Pelvic Reabsorption, to Hydronephrosis and to Accidents of Pyelography, J. A. M. A. **82**:607-613 (Feb. 23) 1914.

Cat 17-1, large, gray.

Aug. 3, 1917, double ligature and division of left ureter.

August 9, loose phenol ligature placed about right. Total phenolsulphonephthalein, 22 per cent.

August 15, left ureter transplanted to bladder. Both ureters were dilated. Though the right was patent, it was more dilated than the completely obstructed left.

August 19, total phenolsulphonephthalein, 45 per cent.

August 25, right nephrectomy.

September 6, total phenolsulphonephthalein, 35 per cent.

November 16, cat well and active. Total phenolsulphonephthalein, 50 per cent.

December 14, cat killed on account of a severe diarrhea. The left kidney was slightly enlarged; it appeared normal macroscopically and showed compensatory hypertrophy microscopically. There was no pelvic residue or dilatation.

We find that the ability of an early hydronephrosis in becoming functionally sufficient after opposite nephrectomy is proportional to the absence or degree of infection or other abnormality present at the time of the repair procedure. It also is dependent somewhat on the nearness of the nephrectomy to the operation of repair. If the animal is allowed a number of days interval (which cannot be prolonged, as shown below) after ureterocystoneostomy before opposite nephrectomy, a somewhat longer period hydronephrosis will recover the ability to perform total function than if the two operations are done simultaneously. Thus, Rautenberg [116] reported successes of a year's duration after twenty-one and twenty-two days hydronephrosis in rabbits on which opposite nephrectomy was not performed for twenty-two and thirty-one days after ureterocystoneostomy. Corbett,[118] however, reports two rabbits with twenty-two and twenty-three days hydronephrosis which lived after simultaneous ureterocystoneostomy and nephrectomy, thirty-nine and fifty-five days, respectively, and were then killed. The repair kidney in one of our own experiments (Dog 22-24, Fig. 16), a twenty-eight day hydronephrosis with thirty day repair period, on gross examination looks perfectly capable of performing total function, but microscopic study reveals such injury as to leave grave doubts of the capability of this kidney in handling a great overload, although a gradual increase of stimulation might reasonably be expected further to increase and perfect the repair processes already instituted, so that eventually it would bear a very great overload. It is certain, however, from results of actual experimentation, that the overwhelming burden of total function is not recoverable by a hydronephrosis of longer duration than three weeks, and the successes, in a two weeks period, will far outnumber those of a three weeks period in a large series (clinical discussion, Part II, Section III).

118. Corbett, J. F.: Changes in Kidney Resulting from Tying of Ureter, Am. J. M. Sc. **144**:568, 1912.

2. Group II of Repair Hydronephrosis: Early period of repair after ureterocystoneostomy in hydronephrosis when opposite kidney is not disturbed. Examination within a few weeks or months after simple ureterocystoneostomy in hydronephrosis up to sixty days' duration shows a condition of repair proportional, as would be expected, to the period of obstruction and the degree of injury from infection. The

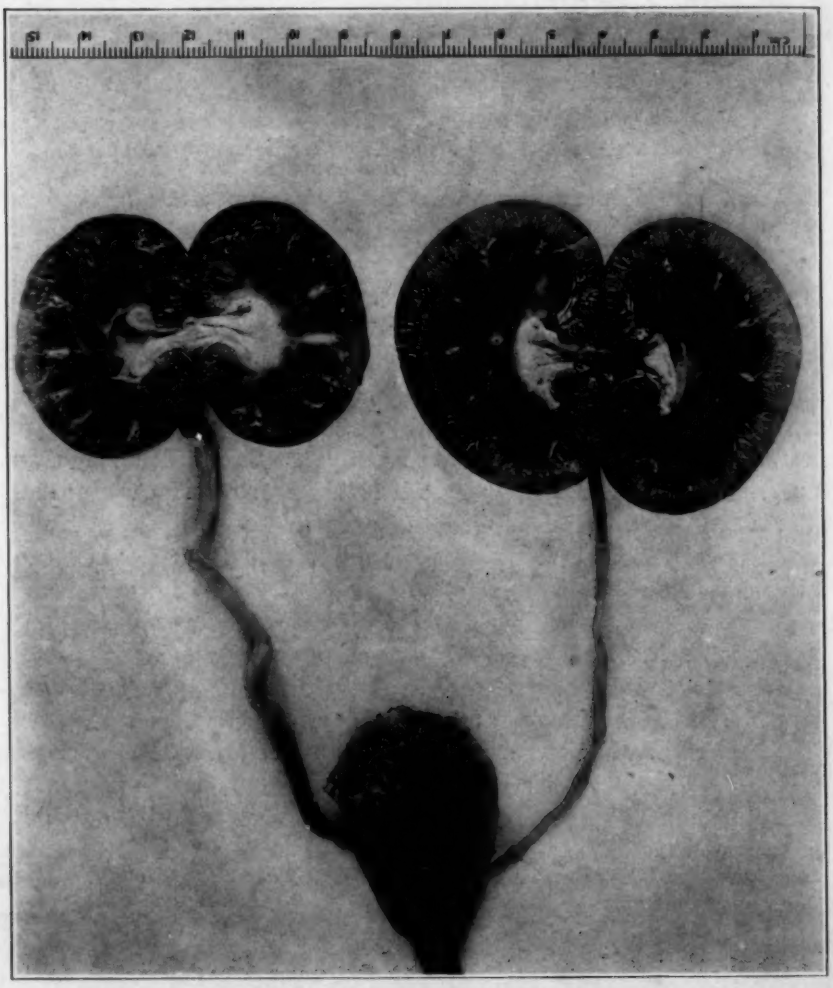

Fig. 16.—Group II repair hydronephrosis; the ureter of the smaller kidney on left had been doubly ligated and divided for twenty-eight days and then the hydro-ureter (Fig. 27, a thirty day simple hydronephrosis in a dog) transplanted to the bladder. Twenty-two days later, the dog was killed and, on examination, the hydronephrotic kidney is seen to have undergone, in twenty-two days, a remarkable degree of repair.

anatomic recovery is marked in a seven or fourteen days hydronephrosis and relatively insignificant in a sixty days one. But, in all the different periods up to about sixty days obstruction, provided the repair procedure was successful and infection absent or mild, groups of hypertrophic radicles will be found. In repair rat kidneys after simple ureterocystoneostomy, there is shrinkage in size, with preservation of kidney shape, and, in the later periods (from forty to sixty days), a uniform grouping of all tubular remnants into one median sagittal repair nodule (Fig. 17). Hydronephroses of more than thirty days obstruction, in dogs, show repair in the form of one, two or sometimes three separate nodules located at the poles or median portion. Figure 18 shows two repair nodules, one at each pole, after fifty-five days repair of a sixty days hydronephrosis. The glomerular and tubular elements of these central or polar lobules show very definite hypertrophic changes, which

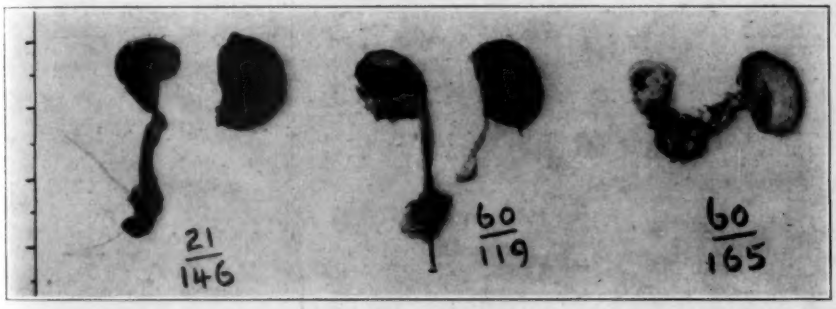

Fig. 17.—Three hydronephrotic repair kidneys (three-fourths size) in rats with their respective hypertrophic mates. There is a median sagittal or central repair nodule present in each. A microphotograph of the middle specimen, sixty day complete ureteral obstruction with 119 day repair period after ureterocystoneostomy, is shown in Figure 12.

are often strikingly circumscribed. In the cat, a single median repair area showing group hypertrophy is usual.

These repair nodules that develop with relief of the obstruction causing hydronephrosis are good examples of group hypertrophy. The less injured renal units attempt to replace the loss of more injured units. The group distribution of hydronephrotic atrophy, in consequence of the blood supply of some portions being more constricted than others, is, of course, the occasion for the occurrence of group repair of the latter as their blood supply is improved on relief of obstruction, as has been beautifully shown by our studies on circulatory changes in hydronephrosis. For a complete understanding of repair hydronephrosis, however, consideration of the permanence of this early group repair under conditions of normal and of extraordinary stimulation is necessary, and these two conditions are discussed below with

reference to Groups III and IV of repair hydronephrosis under Renal Atrophy and Renal Counterbalance.

III. *Summary of Renal Hypertrophy.*—Normal renal tissue subjected to more than an ordinary increase of activity undergoes reparatory changes which differ according to the age when the unusual demand occurs. In the young, anatomic and functional growth is chiefly by hyperplasia or an increase in the number of the secreting radicles; in the adult, wholly by hypertrophy or an increase in size.

Fig. 18.—Group II repair hydronephrosis (Dog 17-66); hydronephrotic kidney with sixty days complete obstruction, fifty-five days repair. There is a repair nodule at either pole. Comparison should be made with the twenty-eight day obstruction with twenty-two days repair (Fig. 18).

Congenital growth by hyperplasia closely parallels in degree the increase in demand, a solitary kidney duplicating the anatomic weight and functional ability of two normal kidneys. In the acquired growth by hypertrophy, the glomerulus and convoluted tubule seem to be the elements most actively concerned, as they show relatively the most growth, Henle's loop being only slightly affected, and therefore a

complete replacement of tissue loss does not occur, the maximum growth of a normal kidney after opposite nephrectomy reaching about two-thirds the size and weight of the two normal kidneys before nephrectomy. The increase in the functional value of such an acquired compensatory hypertrophy is uncertain. According to some, it is closely proportional to the anatomic growth, and, therefore, a complete restoration to the ability of two normal kidneys is not given by the compensatory hypertrophy of one after opposite nephrectomy. Functional ability, like anatomic reparation, is found to be from 60 to 70 per cent. of the normal of two healthy kidneys. According to others, there is a 100 per cent. increase of filtering and absorbing surface and a 100 per cent. functional increase in consequence, even though the total renal mass increase is only two thirds of the normal, but the impossibility of accurate correlation of function with structure renders such studies uncertain. Ordinarily, from twenty-five to thirty days are required for the production of complete anatomic compensation after nephrectomy. The degree of hypertrophy possible is very great, but is relative to the increase in functional demand and the rate of its application. By successive resections, it is possible to remove an amount of renal tissue nearly equal to that of the two original normal kidneys and still have left enough hypertrophic mass to keep the animal alive and in apparent health.

In the acquired conditions of renal growth, three types may be recognized: unilateral mass hypertrophy, bilateral mass hypertrophy and circumscribed or group hypertrophy. The unilateral compensation after nephrectomy or ureteral ligation is typical of mass hypertrophy, but since hypertrophy is relative to an increase of function, any disease or injury with loss of function on one side will lead to a relative mass hypertrophy of its healthy fellow. In some conditions, however, opposite mass hypertrophy fails to develop because of inhibition of reparation through blood borne influences, as in pyonephrosis or infected hydronephrosis.

A bilateral mass hypertrophy in every way similar to the foregoing unilateral can be experimentally produced by bilateral hyperactivity. Bilateral compensatory hypertrophy will follow, for example, a successful ureteroduodenal transplantation, in which, because of complete intestinal reabsorption, a double excretory burden is placed on both kidneys.

A circumscribed or group reparation is manifested in most renal diseases, whether unilateral or bilateral, because the lesion of most diseases is not diffuse but shows a distinctly circumscribed distribution, and the less injured areas, because of relative hyperactivity, undergo reparatory changes while the more injured portions, being in addition

relatively inactive, undergo atrophy. Repair in hydronephrosis is an example of group hypertrophy. Definite renal reparation occurs after removal of the ureteral obstruction, in hydronephrosis up to sixty days complete block, and the degree of reparation is inversely proportional to the period of obstruction and the degree of secondary injury by infection. A hydronephrosis of from two to three weeks, complete ureteral obstruction, is often capable of sufficient restoration completely to compensate for opposite nephrectomy, but death from renal insufficiency invariably follows ureterocystoneostomy and opposite nephrectomy in ureteral obstruction of longer duration. In cases in which the opposite kidney is not removed, a degree of group repair, quite remarkable when compared to the degree of renal injury that is present, for all periods of hydronephrosis up to sixty days is found in the uninfected and most successfully repaired cases in the earlier periods of a few months following the procedure (ureterocystoneostomy) which occasions the repair.

SECTION III. RENAL ATROPHY

1. INTRODUCTION

The diminution in the size of an organ and in its functional activity which were once fully and normally developed either by shrinkage of cells without change of specific cell structure or by loss of cell elements and structure as a result of degenerations constitutes atrophy (Gruber and Bing [70]). Atrophy is an acquired loss of renal tissue [119] and may be due to one or more of several biologic causes, such as inanition, loss of bioplastic energy (senile atrophy), inactivity (disuse atrophy), nerve disturbance or space delimitation (pressure atrophy) (Meckleberg). Atrophy from overwork and overnutrition also are recognized. The commonly described condition of renal loss, however, is degenerative rather than atrophic. Renal degenerations follow the injurious action of bacterial, chemical and other toxins, and are classified into the various retrogressive changes of cloudy swelling and the fatty, amyloid and hyaline degenerations and necroses. The common group distribution of such changes has been emphasized and recognition of unilateral and bilateral group degenerations is to be found in the literature. Simpson (1915) classified contracted kidney into five groups: (1) genuine or primarily contracted kidney; (2) atherosclerotic kidney (patchy sclerosis of Zeigler); (3) secondary contracted kidney (chronic interstitial nephritis); (4) hydronephrotic contracted kidney, and (5) senile kidney. All these forms are retrogressive

119. Aplasia and hypoplasia are congenital types of loss or diminution of renal tissue, and hyperplasia is the compensatory analogue (absence of one kidney, aplasia; infantile kidney, hypoplasia). Hypertrophy is the acquired compensatory complement of atrophy.

metamorphoses and may be explained, except hydronephrotic atrophy, as the result of degenerations or necroses due to the destructive action of toxins or products of disordered metabolism.

It is possible to produce experimentally various types of renal atrophy and degeneration, but a close distinction of the fundamental biologic and pathologic difference is difficult. Simple atrophy has a more general biologic basis, while diminution in size as a result of degeneration and necrosis is more strictly pathologic. Renal hypertrophy in response to hyperfunction is of common knowledge, but we have failed to find mentioned a single instance of even the possibility of renal atrophy from disuse. Pathologists universally explain all types of renal loss as due to some form of direct injury. Hydronephrotic atrophy is recognized as an example of a combination of biologic factors: inanition, anemic atrophy, disuse and pressure, the latter of which is primary (Hinman and Morison [120]). Our injection experiments have shown the fundamental relation of impairment of the circulation (anemia), and it is probable that inanition and disuse are always secondary factors. In the primary atrophy that rarely follows complete ureteral obstruction in some animals, there must be an acute primary anuria, secondary to inanition and anemia, as a result of a profound arterial spasm with atrophy as a result.

The experimental production of a pure disuse renal atrophy is probably impossible, but its significance, as a factor in renal counterbalance, can be emphasized by experiments with hydronephrosis and ureteroduodenostomy.

2. GROUP III REPAIR IN HYDRONEPHROSIS: LATE ATROPHY OF REPAIR NODULES FOLLOWING RELIEF OF OBSTRUCTION, WHEN OPPOSITE KIDNEY IS UNDISTURBED

It has been shown how ureterocystoneostomy in animals with hydronephrosis up to sixty days complete ureteral obstruction is followed by definite and often pronounced reparatory changes of the nature of circumscribed or group hypertrophies (Group II), and how a hydronephrosis of from two to three weeks has sufficient reserve for the restoration of total function after ureterocystoneostomy and opposite nephrectomy (Group I). These changes are not in the strict sense of the word compensatory, as is, for example, the cardiac hypertrophy that follows an aortic insufficiency. Doubt as to their permanency is justifiable. Relief of urinary stasis, theoretically, removes the destructive action of pressure atrophy, of inanition and of disuse, and the hypertrophic and reparatory changes will presumably improve with

120. Hinman, F., and Morison, D. M.: Experimental Study of Circulatory Changes in Hydronephrosis; Preliminary Report Relating to Unilobed Kidney as Instanced in Rabbit, J. Urology **11**:435-452 (May) 1924.

time and exercise. However, it is found experimentally that the best examples of hydronephrotic repair, relative, of course, to the period of ureteral obstruction, are found in the early periods after ureterocystoneostomy (Group II early period). Examination of a thirty days' hydronephrosis from one to two years after ureterocystoneostomy reveals a complete atrophy of what on examination only a few months

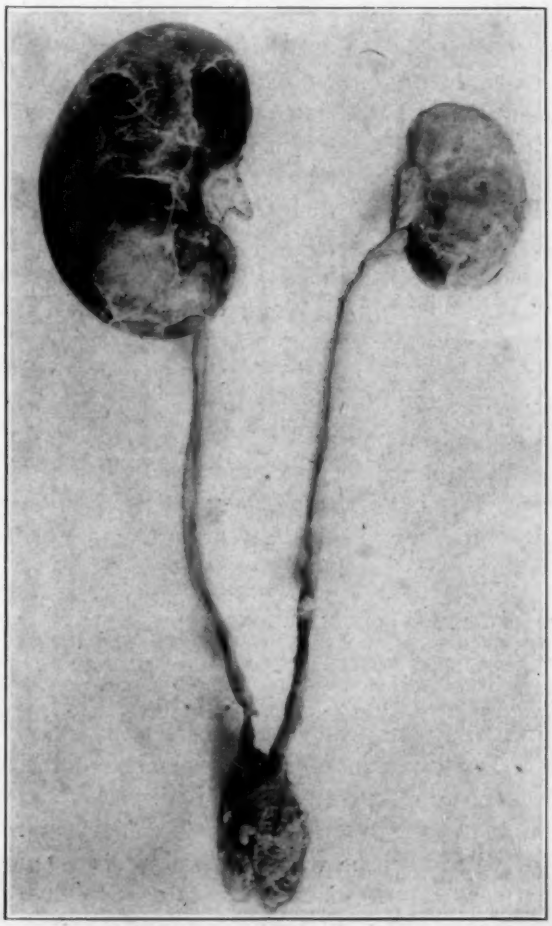

Fig. 19.—Group III repair hydronephrosis; left ureteral obstruction for twenty-one days, when ureterocystoneostomy was performed. Two hundred and forty-nine days later, the dog was killed. There was almost complete atrophy of the left kidney. No infection was present. The ureteral transplant into the bladder was in perfect condition and was freely patent. Comparison should be made with the twenty-eight days obstruction with twenty-two days repair (Fig. 16), and sixty days obstruction with fifty-five days repair (Fig. 18, Group II), and with the thirty-one day hydronephrosis with 338 days repair (Fig. 20, Group IV).

after ureterocystoneostomy, showed a considerable degree of renal reparation. The rather considerable reparatory hypertrophy that at first follows relief of thirty days ureteral obstruction succumbs in from one to two years (and in most instances a two or three weeks obstruction as well), just as completely as does the insignificant repair nodule of a sixty day hydronephrosis. The following protocol illustrates the complete renal atrophy that follows the earlier reparatory changes in long periods after relief of ureteral obstruction (Group III late period).

EXPERIMENT 5.—Late atrophy of hydronephrotic repair; ureteral obstruction of twenty-one days; repair period of 249 days.

Dog 5, weighing 20 pounds (9 kg.).

There was a complete obstruction of the left ureter for twenty-one days. After a ureterocystoneostomy, and a drainage period of 249 days, the urine was free from bacteria and pus. The dog was killed, under ether, with preliminary functional study. The appearance time of phenolsulphonephthalein was four minutes for the right kidney, and eight minutes for the left. In the first fifteen minutes, 25 per cent. of the dye was excreted by the right kidney, and 5 per cent. by the left; in the second fifteen minutes, 20 per cent. by the right kidney and 2.5 per cent. by the left, the total excretion for the first half-hour being 45 per cent. for the right kidney and 7.5 per cent. for the left. At necropsy, the left kidney weighed 15 gm.; the right, 48 gm. The ureter was freely patent. There was no pelvic dilatation on section, and no evidence of infection. Figure 19 shows that the left kidney was reduced to one-third its size, and that, even in the gross, cortical atrophy was quite marked.

This experiment is of interest and most significant when compared to the final results in Dog 22-24, in which a thirty days complete ureteral obstruction showed remarkable repair after twenty-four days (Fig. 16), and in Dog 21-39 in which a thirty days hydronephrosis was found capable of performing total renal work after its compensatory mate had been gradually destroyed by a partial block of its ureter (Fig. 20).

3. LATE ATROPHY OF AN EARLIER HYPERTROPHY FOLLOWING UNILATERAL URETERODUODENOSTOMY

The possibility of successful ureteral transplantation to the duodenum has been shown (Part I, Section II). In successful cases, there is no ascending infection and no damage or injury from urinary back pressure. The transplanted right kidney continues to pour the products of its activity into the duodenum, but because of complete reabsorption the left kidney is burdened with double the work as effectively as if right nephrectomy had been performed, and the left kidney undergoes a complete compensatory hypertrophy just as quickly. In the surgically successful cases of transplantation, it has been demonstrated (Protocol 3) that both kidneys, when examined in from two

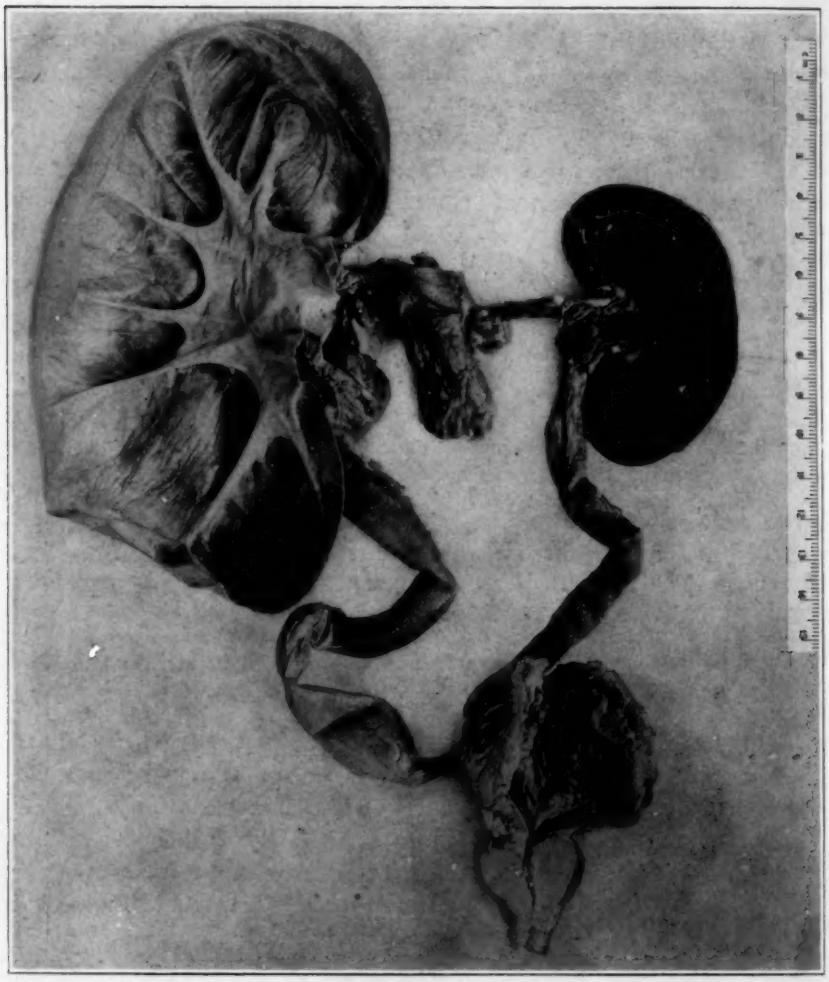

Fig. 20 (Dog 21-39).—Group IV repair hydronephrosis; the left kidney (smaller and darker picture in the photograph) had its ureter ligated for a period of thirty-one days and then transplanted into the bladder. Seven days later, a rubber band was placed about the right ureter in such a way as partially to obstruct it. Three hundred and ninety days later the animal was killed with the findings as shown in the illustration. The thirty-one day left hydronephrosis has undergone a remarkable repair (comparison should be made with Figure 23, a thirty day simple hydronephrosis), whereas the right kidney with its ureter partially obstructed has undergone an almost complete hydronephrotic atrophy, there being only a small parenchymal nodule at its upper pole. Retention and excretion tests were normal before the animal was killed, demonstrating that the thirty-one day hydronephrosis had undergone a complete functional counterbalance with the anatomic readjustment.

to three months, show an equally complete hypertrophy. This is readily explained on reflection that the right has received the same double stimulus for work during this period as the left. The right kidney has remained healthy, uninfected and uninjured by back pressure. Its blood supply has been undisturbed, and the blood carried through it is of the same character as that through the left. The development of a bilateral hypertrophy in the first few months after successful transplantation is the logical consequence. But will the right kidney continue its hyperactivity? Conditions will be different after compensatory hypertrophy of the left kidney (from thirty to forty days) has occurred in that there is not now the same overstimulus to work as at first. Conditions of inhibition also are supplied by the unphysiologic position of the ureter. Even though evidence of back pressure is lacking, the active intestinal movements would be apt to set up antiperistaltic waves in the ureter, with their effects of functional inhibition. An occasional reflux of duodenal contents might cause reflex inhibition, so that, even though actual injury to the renal tissue does not occur, the lessened stimulation and increased inhibition of function on the right side as compared to the left produce a marked biologic inequality between them. Hyperactivity on one side and relative inactivity on the other will, in time, show their effects.

In four experiments, the late results of ureteroduodenostomy after 443, 381, 409 and 288 days, respectively, were studied. The results of bilateral hypertrophy after an earlier period of transplantation have been given (Part I, Section II). The change from early hypertrophy to late atrophy is gradual and no doubt, judging from the different degrees of atrophy for the relatively similar late periods, there is variability in the factors producing it. This experimental demonstration is not given as an example of renal counterbalance, for it is not an example, and discussion of its particular physiologic significance may only tend to confuse our main argument to which it is unrelated. The late atrophy of repair hydronephrosis occurs under biologic conditions fundamentally different from those of the late atrophy following ureteroduodenostomy. Injury plus inactivity causes the former. As to the cause of the latter, we can offer no proof, but some food for thought perhaps in the conception that this late atrophy following ureteroduodenostomy is likewise largely a disuse atrophy. Its presentation therefore is in illustration of renal atrophy and not of renal counterbalance.

EXPERIMENT 6.—Right ureteroduodenostomy of 409 days' standing, showing late renal atrophy.

Dog 6, a short haired, black, male mongrel, weighing 24 pounds (10.9 kg.). Oct. 25, 1920, right ureteroduodenostomy.

Oct. 29, 1921, blood urea nitrogen, 26 mg. per hundred cubic centimeters; non-protein nitrogen, 50 mg. per hundred cubic centimeters.

Jan. 4, 1922, blood urea nitrogen, 21 mg. per hundred cubic centimeters; non-protein nitrogen, 39 mg. per hundred cubic centimeters.

January 7, killed with ether.

Necropsy: The abdominal sheen was normal in appearance. There were no adhesions present. The left kidney was large but normal in all other respects. The right kidney was exceedingly small and almost buried in its fatty capsule. Its ureter was little, if any, larger than normal and issued from a small, undilated

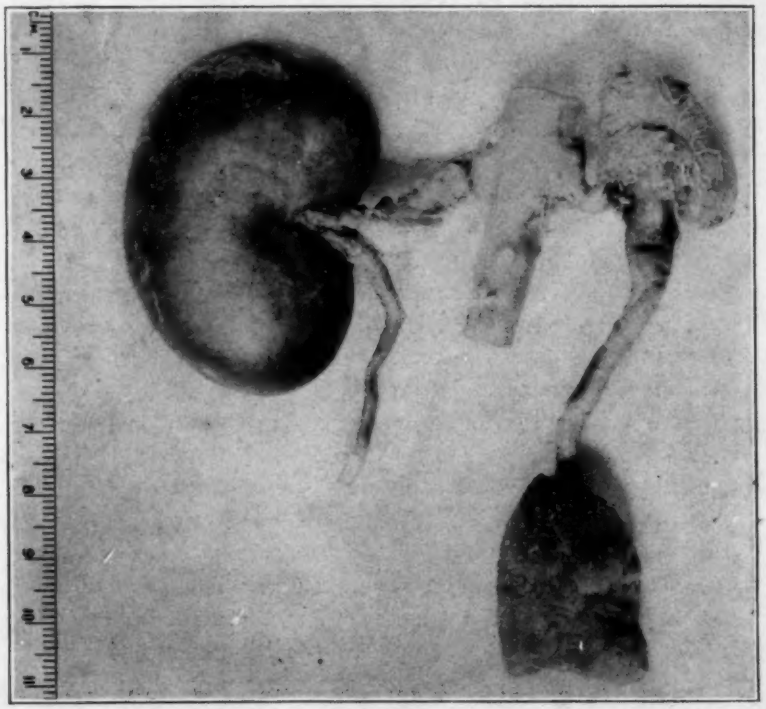

Fig. 21. (Dog 21-37).—Left and right kidneys (three-fourths size) 409 days after right ureteroduodenostomy. The left kidney is healthy and hypertrophic. The right side shows marked atrophy with preservation of shape, and the ureteral opening into the duodenum is freely patent.

pelvis, which held about 1.5 c.c. of fluid. The duodenal end projected into the duodenum in a mucosa covered papilla. Fluid could be forced through this papilla with great ease into the duodenum (Fig. 21).

Kidney measurements:	Weight	Length	Width	Depth
Right kidney	5.4 gm.	2.7 cm.	1.28 cm.	1.4 cm.
Left kidney	39.0 gm.	5.6 cm.	2.9 cm.	2.9 cm.

Microscopic Findings: Microscopic examination of the right kidney showed advanced diffuse changes throughout such as one sees in advanced chronic diffuse nephritis. In the sections examined, no glomeruli were seen which appeared quite normal, the vast majority of them showing advanced hyaline and sclerotic

changes and obliteration. The blood vessels exhibited a marked degree of intimal alteration and thickening. The tubules were shrunken and collapsed, their epithelium degenerated or entirely lacking, and large areas were seen in which the last vestiges or tubular remnants were replaced by uniform fibrous tissue. The cortex and medulla were markedly thinned out. In the centers of many of these fibrous areas were seen groups of large tubules possessing wide lumens and lined by one or more rows of hyperplastic epithelium showing occasional mitotic figures. In one area near the surface of the cortex, a compensatory nodule of active cortical tissue was seen. A slight degree of lymphocytic infiltration was present in some parts of the cortex and medulla. Beneath the pelvic mucosa was seen a dense infiltration with lymphocytes and plasma cells and occasional neutrophils (Fig. 22).

Microscopic examination of the left kidney showed normal renal tissue exhibiting a picture of marked hypertrophy. The glomeruli were large and cellular looking, but probably not out of the ordinary. The tubules exhibited a marked degree of activity, especially the convoluted and Henle tubules. The nuclei were hyperchromatic and showed occasional mitoses. The blood vessel walls appeared normal. There was no evidence of active acute or chronic inflammation (Thomas E. Gibson, M.D.)

EXPERIMENT 7.—Right ureteroduodenostomy of 288 days' duration, showing beginning renal atrophy and in which a relative functional test and a secretory pressure determination were made before the animal was killed.

Dog 7, a large, male shepherd, weighing 47 pounds (21.3 kg.).

March 7, 1922, urine (catheterized) clear; trace of albumin; no pus or blood.

March 9, right ureteroduodenostomy.

December 14, dog had been and was in excellent condition, was playful and good-natured.

9:15, given morphin, one-fourth grain (0.16 gm.) hypodermically.

10:15, 300 c.c. of water by stomach tube.

11:00, ether.

The following experiment, in collaboration with Dr. R. K. Lee-Brown and in prosecution of a study of renal resorption, was performed. The two ureters were exposed near their respective pelves by lumbar incision. The right ureter was practically normal and not dilated, and it was seen that its opening into the duodenum was freely patent. A simple glass cannula was thrust into it through a small slit and firmly tied in position. Urine began to flow almost immediately through this cannula, and pressure over the kidney showed that this was secretory and not due to pelvic retention. This cannula was attached to a glass tube of some 100 cm. length which was placed perpendicularly so as to act as a manometer for the registration of secretory pressure in centimeters of urine. Into the opposite ureter was tied a specially constructed two-way cannula, one arm leading to a similar glass tube for the registering of secretory pressure, the other carrying through an ordinary cystoscopic rubber tip on its end a 4F Albarran flute-end ureteral catheter which was of such small size relative to the lumen of its cannula and its two arms that it could be pushed on through into the kidney pelvis without obstructing the outflow of urine through the cannula and by way of its other arm into the glass tubing manometer. The purpose of the catheter was to enable thorough lavage and cleansing of the pelvis, so as to replace the urine in it with any solution desired (in this case, a solution of phenolsulphonephthalein containing 60 mg. per cubic centimeter). The secretory pressure of the two kidneys, as measured by the height to which the urine secreted by each rose in

the two tubes, had produced, at 1:50 p. m., a column of urine 64 cm. in height, on the right, and 78 cm. in height, on the left. (The maximum secretory pressure is reached in about four hours.) At 2 p. m., the manometer was disconnected with the cannula in the right ureter and urine allowed to drain freely from the open arm into test tubes. The left manometer was emptied of its urinary content, the kidney pelvis on this side washed free of urine, by means of the ureteral catheter which had been pushed on up into it, and then, after the manometer was reconnected, a solution of phenolsulphonephthalein, 60 mg. per cubic centi-

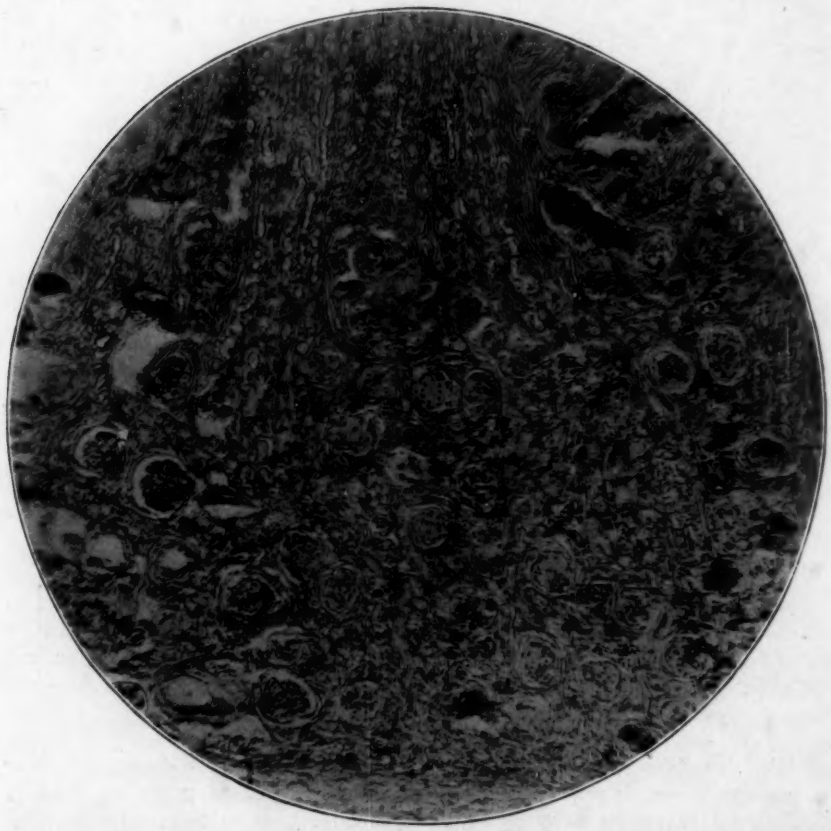

Fig. 22.—Microphotograph of right kidney shown in Figure 20, atrophied after 409 days transplantation of the ureter into the duodenum. The very marked connective tissue infiltration and complete atrophy of tubules is evident. Glomeruli have undergone considerable hyaline degeneration. There is some small round cell infiltration.

meter, was slowly injected through the catheter until it rose in the manometer to a height of 64 cm. The catheter was then withdrawn into its respective cannular arm so as to leave the cannula and the other arm leading to the manometer free. At 2:30, the column of phenolsulphonephthalein had been raised to a height of 80 cm. (maximum secretory pressure), about which point it fluctuated with inspiration and expiration for a few minutes, but then began gradually to fall

so that, at 3 p. m., it was around 65 cm. in height. At the time phenolsulphonephthalein was substituted for urine in the left manometer (2 p. m.), a fresh test tube with a few drops of sodium hydroxid was placed under the end of the right cannula. Phenolsulphonephthalein appeared in this test tube in considerable concentration within a few minutes. This phenolsulphonephthalein in order thus to appear had to gain entrance to the circulation by reabsorption from the left kidney pelvis at secretory pressure, and be secreted by the right kidney which had been functioning into the duodenum for 288 days. At 3 p. m., when the height of the phenolsulphonephthalein column had fallen to 65 cm. (from a maximum of 80 at 2:30), the left manometer also was disconnected and the left kidney pelvis again washed thoroughly clean, this time of phenolsulphonephthalein, by means of sterile water injection through the ureteral catheter after its reinsertion into the pelvis. Both cannulas were now allowed to drain freely into test tubes for twenty minutes, in which time there was collected from the right kidney 8 c.c. of urine containing 2 per cent. phenolsulphonephthalein, and from the left kidney 14 c.c. of urine containing 5 per cent. phenolsulphonephthalein.

Necropsy: The right kidney weighed 39 gm., the left 59.5 gm.

4. COMMENT ON EXPERIMENTS WITH URETERODUODENOSTOMY

The anatomic changes that follow successful right-sided ureteroduodenostomy present an interesting problem for explanation. In the first few months, bilateral reparatory hypertrophy occurs. The functional integrity of the right kidney, in this period of hypertrophy, has been demonstrated, and even in the late periods it is occasionally found at work, though inefficiently. There has been no disturbance of its nervous or blood supply. Infection and back pressure are absent. Therefore, why should not its early and healthy hypertrophic condition persist indefinitely? The fact remains that conditions at necropsy are quite different when an animal with a successful right ureteroduodenal transplant is allowed to live for one or more years than when it is killed after from two to three months. The right kidney, in the late period, will be found to have undergone a marked or even complete atrophy, whereas the left kidney will be in no way dissimilar to that in the previous experiment in which the animal is killed in the early period.

The explanation of the early hypertrophy of the right kidney following transplantation of the ureter into the duodenum seems obvious. It is burdened with the same double load as its undisturbed mate, and it is natural that it should undergo a similar hypertrophy. But the reason for the late atrophy is not so simple. The fact that this kidney is not needed under present conditions, the left being fully compensatory, fails to explain satisfactorily its atrophy. It was just as unnecessary to total function during the early period of transplantation in which it hypertrophied, and no parallel of similar cerebration of an organ as would be thus required by such an explanation is known. Injury to the kidney, by back pressure from constriction of the ureteroduodenal orifice, by

reflex of duodenal contents, by bacterial toxins, by disturbance of the complex neuromusculature of the ureter, or by the peristaltic action of the intestinal wall into which the ureter opens, alone or in combination, likewise fail clearly and completely to explain this late atrophy. Injury from back pressure cannot be demonstrated. The condition is totally different from an hydronephrotic atrophy. The ureters of these transplanted kidneys are not dilated, and it is a proved fact that hydroureters do not recover their normal appearance after relief of obstruction. Even should a regurgitation or reflux of duodenal contents occur, and it has not been demonstrated, it is unlikely that such marked atrophy would result. Active infection is not found in the stage of early hypertrophy or that of late atrophy. Transplantation of the ureter to the rectum or the bladder produces no such atrophic changes. Injury from any or all of these factors would seem to fall short of a clear explanation in view of the early and complete hypertrophy in spite of it.

The explanation approaches a more fundamentally biologic principle than that of direct injury. Just as increased renal activity produces renal hypertrophy, so diminished activity or inactivity will produce renal atrophy. Such atrophy would exemplify a disuse atrophy. No reference by pathologists or others has come to our attention of a disuse atrophy of renal tissue. Differences in tissue resistance to the injurious action of even a moderate bacterial toxin over a long period as a necessary sequence to differences in tissue activity and inactivity must not be overlooked, and would undoubtedly tend to hasten an atrophy of disuse, if nothing more. The appearance of renal fibrosis, in some of these late atrophies, and the marked interstitial changes present, closely simulate the chronic fibrosis of old nephritis and arteriosclerotic changes, and the marked difference of relative preservation in two experiments (Dogs 21-35 and 22-42) as compared to the complete destruction of two others (Dogs 21-38 and 21-37) is disconcerting. Evidence of infection is found in the two latter experiments, and this greater injury may account for the difference. Infection may have also been present though less pronounced in the two former and so account also for their atrophy of a lesser degree, but we are not content to accept injury either of infection or other cause as the sole factor in these cases of late atrophy.

Many and various factors produce inhibition of renal activity without direct injury to renal tissue (Renal Inhibition, Part II, Section I). Two normal kidneys do not function uniformly to the same degree, even though the blood passing through them is of uniform quality. First one, then the other will rest for a short period, although the work performed by each will be about equal over long periods. Experience in functional work after ureteral catheterization leaves no room to doubt

this inequality of activity for short periods (Kapsammer,[121] Keyes and Stevens[122]). The factors which produce a variation in functional response to an equal stimulation are poorly understood. Watching the irregular activity of different glomeruli of the frog's kidney through a binocular microscope illustrates this variation even for the individual radicles of the kidney; as, of two tufts side by side, one may have blood rapidly coursing through its capillaries, while the stream in the other is barely perceptible or even perfectly quiescent and, in the next moment, conditions are reversed or altogether different. In the case of two normal kidneys, work is evenly apportioned. Inhibition on the part of one or both sides leaves more work for both kidneys later. In the experiment under discussion, this balance has been destroyed. Inhibition on the part of the left kidney produces added stimulation to both later, but inhibition of the right would have no effect on the work required of it or its fellow later, as it works in a circle, all products of its activity being poured back into the circulation. Whether it is active or inactive has no effect on the left kidney, on which total excretion is solely dependent. The activity or inactivity of the left kidney would have its effect on the right merely by reason of the load of excretory stimuli in the blood. During the early period when bilateral compensation occurs, hyperstimulation is present for both, and both kidneys hypertrophy. Once the left becomes accustomed to all the work, the right is more subject to the influence of minor factors of inhibition of its activity and the left less so. Previous to left hypertrophy, the somewhat higher level of stimulation in the blood reacted more evenly on both. After left hypertrophy, disturbance of the right, whether it is through the ureteral neuromusculature, the reflex action of intestinal peristalsis or possibly reflux of duodenal contents, or otherwise, may now have a decided inhibitory action on its activity, and being nonessential to total function, longer and longer rest periods will be followed by a lower and lower ability to respond equally to the same stimuli as formerly. Greater stimulation being impossible in view of the competent activity of the left kidney, the right will succumb more and more to inhibitory influences and become less and less active until it becomes unable to respond at all to ordinary stimuli, ceases function and gradually atrophies from disuse. This idea for the sake of clearness may be diagrammatically represented as in Figure 23.

In Table 6 are listed some original experiments with ureteroduodenal transplantation. In Experiments 1 to 9 is demonstrated the

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121. Kapsammer, G.: Ueber Kryoskopie und reflektorische Polyurie, Wien. klin. Wchnschr. **17**:97-102, 1904.

122. Keyes, Jr., and Stevens: Intravenous Administration of Phenolsulphonephthalein for Ureteral Catheter Study of Renal Function, New York M. J. **95**:1134, 1912.

fatal result of bilateral transplantation or of unilateral when there is only one kidney. Duration of life afterward corresponds to that following bilateral nephrectomy, from nine to ten days. Dog 17-66 lived a fortnight longer on a sixty day repair hydronephrosis and died of distemper. The fact that death may be averted by skin transplantation is

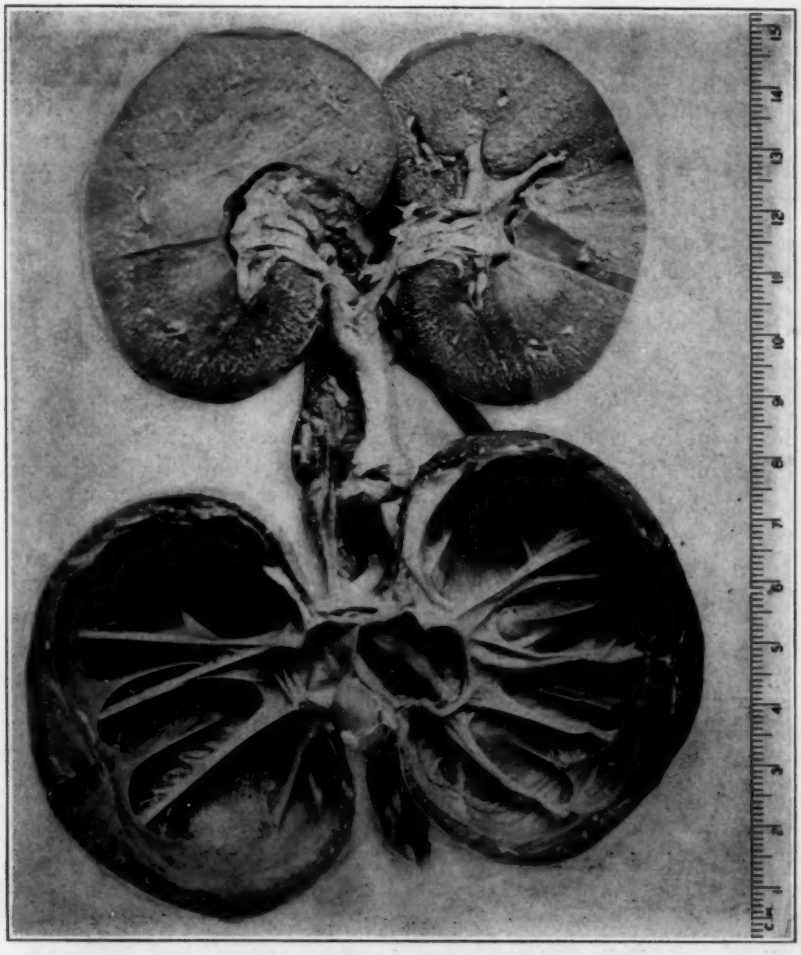

Fig. 23 (Dog 22-39).—Simple hydronephrosis of thirty days complete ureteral obstruction, with its opposite hypertrophic kidney; to be compared with Figure 20 of Group IV of repair hydronephrosis, Figure 16 of Group II, and with Figure 19 of Group III.

shown by Experiments 11, 12 and 13. These experiments and the functional studies of Experiments 10 and 16 establish the existence of a continuation of activity on the part of the transplant during its hypertrophic and atrophic periods. Some of these experiments show the

incidence of back pressure or of infection following faulty transplantation, but the majority are surgically successful by their absence, and, in these animals, bilateral hypertrophy always occurs as the first change. Experiments 15, 16, 17 and 18 show that late renal atrophy of the transplant invariably follows prolongation of life for from one to two years. There is an early bilateral hypertrophy and a late unilateral atrophy. A study of the gross and microscopic pictures of Experiments 13 and 16, in both of which evidence of back pressure and of infection is entirely wanting, is particularly convincing of disuse being a factor, although atrophy is the least pronounced.

5. SUMMARY OF RENAL ATROPHY

Loss of renal substance may be congenital or acquired. Agenesis, aplasia and hypoplasia are congenital conditions. Acquired retrogressive changes of renal tissue follow both biologic and pathologic conditions, and as such are atrophic or degenerative. Inanition, functional disuse and limitation of space (pressure) are common, senility and overwork, uncommon biologic factors. Enervation, in that it does not lead to inanition and functional disuse, is not a factor in renal atrophy. Parenchymatous, fatty, amyloid and hyaline degenerations are the pathologic results of both biologic and disease conditions. It is rarely possible to distinguish by the result all the fundamental causes. A true disuse renal atrophy has never been recognized. It is probably always secondary to some primary factor, as even in ordinary inflammation (rubor, calor, dolor, tumor and loss of function), but its significance to renal changes has been heretofore insufficiently emphasized. The early and considerable reparation of a few weeks hydronephrosis, which may become complete and permanent on opposite nephrectomy, is usually found after a long period (from one to two years) to have undergone almost if not complete atrophy when accompanied by a healthy compensatory mate. The early hypertrophy of a right kidney after right-sided ureteroduodenostomy, which is in every way equal and similar to the complete compensatory hypertrophy of the undisturbed left kidney, is found after a period of from one to two years to have undergone atrophy. The unilateral atrophy of neither of these experiments is satisfactorily explained purely by degenerative changes. The presence and condition of the active and compensatory opposite kidney in the hydronephrosis experiments seem definitely to have an influence on its progress and development. The nature of this influence will be discussed under renal counterbalance. The late atrophy after ureteroduodenostomy should be disregarded in this connection. Discussion of it has already been made.

SECTION IV. RENAL COUNTERBALANCE

1. INTRODUCTION

The relative place of atrophy, whether in consequence of insufficient activity or of progressive degeneration in the sense of Rautenberg,[116] as a result of the injury of primary hydronephrosis in the late loss of renal substance following an earlier repair after ureterocystoneostomy may be demonstrated by a shift in the functional demand on the two sides. If the process is a true toxic and progressive degeneration, then an increase in the functional demand should have little if any influence on it, and in fact might hasten the destruction. But if the local resistance of tissues varies with relative inactivity and activity, increasing the activity of an injured renal mass may either raise the resistance so as to nullify the degenerative process or so overwhelm it (fatigue) as to hasten its destruction. These considerations are well illustrated by the following experiment.

2. GROUP IV REPAIR HYDRONEPHROSIS: HYDRONEPHROTIC REPAIR AND COUNTERBALANCE WHEN OPPOSITE KIDNEY IS GRADUALLY DESTROYED BY PARTIAL URETERAL OBSTRUCTION

A gradual injury of the complete compensatory kidney can be produced simply by a partial obstruction of its ureter with a rubber band. In a year's time, varying with the degree of obstruction, it will have undergone practically a complete hydronephrotic atrophy of its previous hypertrophic tissues. To all intents and purposes this kidney, which previously was doing all the work, is now a dead kidney, and the animal, provided the degeneration instituted by the thirty days hydronephrosis of the opposite side has proceeded as it did in the other experiments in which the compensatory kidney was undisturbed, will have no secreting renal tissue at all. Death from renal insufficiency would then surely result. But it does not, for the gradual increase in functional demand so progressively stimulates a potentially capable kidney that it regains not only its lost ability but also hypertrophies to such an extent that it now easily and successfully carries the burden of total renal work, and itself becomes the compensatory kidney. The following protocol demonstrates the point in question.

EXPERIMENT 8.—Thirty days left hydronephrosis; left ureterocystoneostomy; seven days later, partial obstruction of right ureter. Killed in 390 days.

Dog 8, a male shepherd, weighing 42 pounds (19.1 kg.).

Nov. 1, 1920, ligation of left ureter.

Blood urea nitrogen, 18 mg. per hundred cubic centimeters; nonprotein nitrogen, 34 mg. per hundred cubic centimeters; phenolsulphonephthalein 70 per cent. in two hours. The abdomen was opened in a midline incision under the usual ether anesthesia and aseptic precautions. The incision extended from the symphysis pubis upward about 4 cm. The bladder was seized with the fingers

and drawn gently upward into the wound. A double silk suture was passed beneath the left ureter just above its junction with the bladder, and with it the ureter was firmly and doubly ligated. The ureter was severed between these two ligatures, and the stumps were dropped back into the wound. The abdominal wound was closed with No. 2 chromic sutures. During the next week, the dog made an uneventful recovery.

December 2, left ureterocystoneostomy. Under ether anesthesia and aseptic precautions, the abdomen was opened in the midline. The bladder was lifted up into the wound, and the large, tortuous left hydro-ureter was seen. It was approximately 1 cm. in diameter and filled tightly with urine. The end of the ureter was carefully freed from its bed, and about 100 c.c. of slightly smoky urine was drained into a large test tube when the ligated tip was cut off. A No. 00 catgut suture was then passed through the adventitia of the ureter which was slit open for about one-half centimeter on the side opposite to the suture, the free ends of which were threaded into small milliner's needles. A short incision was then made through the bladder wall in its posterior aspect just a little lateral to the midline, and the threaded milliner's needles passed through this and out through the bladder wall about 1 cm. above their point of entry, where they appeared with a 3 mm. space between them. Traction on the catgut drew the ureter through the bladder wall, and, when the ends of the fine catgut were tied, the ureter was held with its slit end open within the bladder. The ureter was more firmly fixed to the bladder wall externally with five interrupted stay sutures, which pierced the adventitia of the ureter and the external coats of the bladder. The abdominal wound was closed with No. 2 chromic sutures. Recovery was prompt and without incident.

December 9, partial ligation of right ureter. Under ether anesthesia and surgical asepsis, the abdomen was opened in the midline just below the umbilicus.

The peritoneum was smooth and glistening. There were few adhesions in the region of the bladder vault. The right ureter was identified in its bed as low down as possible without disturbing the recent operative area behind the bladder. A short length of ureter was freed in an area about 3 cm. from its point of entry into the bladder, and a rubber band 2 mm. wide was placed around it and stretched. The ends of the band thus stretched were tied with silk so as to form a moderate constriction of the ureter. The wound was closed with No. 2 chromic sutures. The animal recovered slowly from the operation, eating little for four or five days. The wound healed readily, however. A period in which its condition slowly improved then followed, lasting from five to six days, during which he lay very still in his cage. Following this, he slowly grew better. A month after operation, he seemed quite normal and ate normal amounts.

Nov. 29, 1921, blood from the jugular vein for nitrogen partition showed: urea nitrogen, 26 mg. per hundred cubic centimeters; nonprotein nitrogen, 49 mg. per hundred cubic centimeters, and creatinin 1.93 mg. per hundred cubic centimeters.

Jan. 4, 1922, killed. Necropsy: The dog was in excellent condition; the weight was 42.5 pounds (19.3 kg.). The coat was long and glossy. The animal had been passing well formed stools and clear urine. Phenolsulphonephthalein, the first hour, was 53 per cent.; the second hour, 20 per cent. Blood urea nitrogen was 21 mg. per hundred cubic centimeters; nonprotein nitrogen, 41 mg. per hundred cubic centimeters. The dog was killed with ether.

There were three operative scars on the abdominal wall, one on each side and parallel to the penis and one in the midline above the penis. The wound areas were all tightly closed and uninfected. There were some scant adhesions

to the under surface of each of the abdominal wounds. The mesentery only was adherent here. The abdominal organs, except for the genito-urinary tract, presented no lesions whatever. The heart was not enlarged and showed no pathologic alterations. The lungs were clear. A sample of urine from the right ureter was clear and showed a considerable amount of pigment. The urine from the left ureter was cloudy. It showed an equal amount of pigment. The urinary tract is shown in Figure 20.

The left kidney was normal in shape and slightly enlarged. It collapsed readily at the hilum with pressure, showing a slight degree of hydronephrosis. The ureter of the kidney was very large, being 1 cm. in diameter. It was not tortuous. Its opening lay in the midline of the bladder posteriorly and was fully patent. It readily admitted a No. 8 F catheter. This kidney showed a heavy venous network over its surface external to the capsule. The right kidney was very large and had a very thin wall. There was a crescentic nodule of parenchyma at its upper pole 1½ cm. thick and 7 cm. long. In all other areas, the wall was of paper thinness. The ureter was slightly larger than that of the opposite side. It was 1.3 cm. in diameter. It was much thinner than the left ureter and very tortuous. Near the bladder, it presented an obstructed area, at which point the rubber band, placed Dec. 9, 1920, was localized. Beyond this, it was of normal diameter. The right ureterovesical orifice through which this ureter opened was normal in all respects and readily admitted a No. 4F catheter. Gentle pressure on the hydronephrotic sac caused a flow of fluid through this ureteral orifice. The wall of the bladder was normal in appearance. The urethra presented no constrictions nor abnormalities. The respective sizes and weights of the two kidneys were as follows:

	Length (Pole to Pole)	Width (Side to Side)	Depth (Hilum to Greater Curve)	Weight	Pelvic Capacity
Left kidney	6.95 cm.	2.5 cm.	3.0 cm.	47 gm.	5 c.c.
Right kidney	16.00 cm.	8.0 cm.	7.5 cm.	52 gm. (empty)	400 c.c.

The nitrogen content of the urine from the left kidney was: urea nitrogen, 0.0045 gm. in 1 c.c.; nonprotein nitrogen, 0.0065 gm. in 1 c.c. The nitrogen content of the urine from the right kidney was: urea nitrogen, 0.0039 gm. in 1 c.c.; nonprotein nitrogen, 0.0068 gm. in 1 c.c.

The total renal work had been gradually transferred, in the foregoing experiment, from the right compensatory hypertrophic kidney to the left hydronephrotic repair kidney. The latter kidney, injured by thirty days complete ureteral obstruction, had responded to the gradually increasing demand in a wonderful manner. The right kidney had meanwhile itself undergone almost complete hydronephrotic atrophy. The experiment illustrates a final anatomic readjustment. The degree of reparation is more impressive if this repair kidney is compared to what it was at the end of the thirty day period of obstruction, as shown in Figure 23, a simple hydronephrosis of thirty days in a dog, a degree of hydronephrosis totally incapable of sufficient repair to maintain life after opposite nephrectomy.

3. EXPERIMENTS ON REPAIR HYDRONEPHROSIS RELATIVE TO RENAL COUNTERBALANCE

The many facts and factors that have been presented relative to renal reserve, reparatory renal hypertrophy and renal atrophy or degeneration bear a close relationship to renal counterbalance. A shift of the burden of the work of excretion from one part or position to another is dependent on the relative efficiency of each. Changes in total amount of work when all renal tissue is uniformly capable results in uniform or cooperative growth or atrophy, but when injury, disease or inhibition affects one part or portion more than another, an unequal or competitive type of response results. The anatomic division of the renal mass into a right and left kidney occasions a marked frequency of unilateral lesions and injuries. The necessity of an anatomic counterbalance between the two sides following the alteration in the functional demand as a result of the injury is obvious. Certain diseased or inhibited renal tissues, which may fail to respond to the ordinary stimulus, will exhibit marked growth and reparation when an unusual stimulus or demand arises, provided this hyperactivity is so gradually placed as not to overwhelm it by fatigue. Demonstration of this fact (Protocol 19) proves that renal atrophy is not wholly a true toxic degeneration but is largely a disuse atrophy in consequence of insufficient functional stimulation.

A very close analogy has been experimentally demonstrated for the liver by Rous and Larimore: [32]

> The occlusion of portal branches to a part of the liver of the rabbit leads to a progressive and ultimately complete atrophy of the parenchyma in the region deprived of portal blood, and to hypertrophy of the rest of the hepatic tissue which receives such blood in excess. Three fourths of the liver may thus be reduced to a fibrous tag within two months, while the remaining fourth attains the bulk of the entire original organ. The atrophy is simple, unaccompanied by obvious degenerative changes or by any connective tissue replacement. More important, it is conditional in nature, failing to progress when the bile duct from the proliferating tissue is ligated and its hypertrophy checked in this way.
>
> There are indications in the literature that an atrophy conditional on hypertrophy, such as is here described, occurs in man after local portal occlusion. And some experiments in our laboratory, not yet completed, show definitely its occurrence in the dog. The changes take place slowly in the canine liver. After three months, the tissue deprived of portal blood has diminished to about one third of its original bulk. The conditional character of the atrophy is proved by its failure to occur to any similar degree in the absence of a compensating parenchyma, as when the portal stream is diverted from the whole liver by way of an Eck fistula.
>
> Is the atrophy functional? If so, its completeness would indicate that the liver has no essential activity—none on which its maintenance depends—that it is not intimately connected with substances derived from organs drained by the portal system. Observations on the rate of hypertrophy after local diversion of the portal stream and on the character of the bile secreted by the atrophic tissue

may be taken to favor such a view. The hypertrophy is nearly, perhaps quite as rapid as if the tissue deprived of portal blood had been removed from the body. The bile secreted from a liver mass far advanced in atrophy and competing with a large bulk of parenchyma that receives the entire portal stream is almost colorless and may give but a weak Pettenkofer reaction. Glycogen, on the other hand, is present in the atrophic cells in approximately the same amount and distribution as in the hypertrophic liver tissue of the same animal.

The fact that a parenchymal shift follows local disturbance in the portal stream has a bearing on the cause of certain alterations in the shape of the normal liver that have been loosely attributed heretofore to pressure from the surrounding organs. It also has some interest in connection with pathological changes. Liver hypertrophy dependent on a preceding destruction has long been known to pathologists. Now a type of destruction dependent on compensatory hypertrophy must also be reckoned with. The occurrence of changes of the latter character will explain certain of the lesions observed in diseases that involve a disturbance of the portal flow to portions of the liver substance.

The various types of experiments with hydronephrosis illustrate these points for the kidney (Table 9). Relief of obstruction of a thirty day hydronephrosis is followed at first (from one to three months) by pronounced evidence of renal reparation and restoration of function, but later (from one to two years) by complete atrophy. The healthy hypertrophic side counterbalances in from twenty-five to thirty days the loss of its weaker mate, and becomes fully capable of performing total function. Sufficient stimulation for the full development and preservation of the reserve power on the hydronephrotic side is lacking because of the more active response of the healthy tissue of the opposite hypertrophic kidney. It is somewhat like the overflow from a dam in which one outlet is just a little lower and larger than the other. All the water flows out the lower side unless the lake rises so fast as to bring its level above the higher outlet, or a dam or obstruction of the lower opening arises. An animal cannot live after opposite nephrectomy, with a repair hydronephrosis of longer than from two to three weeks. Any repair hydronephrosis, even of two weeks, will usually eventuate in complete atrophy if the opposite kidney remains healthy and undisturbed, but even the more pronounced injury of a thirty days hydronephrotic atrophy is capable of complete reparation, if there is a gradually increasing demand for it, as produced by a partial obstruction of the compensatory side. These facts mean that the anatomic readjustment of renal tissue follows somewhat the law of natural selection or survival of the fittest, and have a tremendous significance in relation to conservative renal surgery.

In Table 9 are listed most of our experiments on repair hydronephrosis. Group I demonstrates the insufficiency of renal reparation to meet the sudden overwhelming burden of opposite nephrectomy. Group II shows the degree of early reparation that is possible in hydro-

nephrosis up to sixty days complete ureteral obstruction when working with a healthy mate and emphasizes the inhibitory and degenerative influence of a concomitant infection. Group III shows the ultimate atrophy of these earlier repair kidneys when placed in prolonged competition with a hypertrophic kidney which has been undisturbed, and Group IV the potential strength of a repair hydronephrosis when a distinct but progressive need for its preservation is brought about by a gradual destruction of the opposite compensatory mate.

4. SUMMARY OF RENAL COUNTERBALANCE

The foregoing experiments demonstrate the occurrence of renal counterbalance, illustrate the interrelationship of a functional and an anatomic reserve, and show the slow, progressive nature of anatomic reparation and atrophy, which may be complete only after many months or years. They emphasize the fact that the anatomic is the only type of counterbalance for serious consideration surgically, and that, in the establishment of this anatomic counterbalance, three factors demand consideration: renal reserve power, reparatory hypertrophy and disuse atrophy.

Renal reserve refers to the potential strength or power of renal tissue to perform more work on demand. Native or static functional reserve is limited, and, when the demand surpasses this limit, hypertrophy to a relative though limited degree occurs. This ability to hypertrophy on demand may be called the compensatory reserve of renal tissue, and if this compensatory ability is competent, renal cells will overcompensate and thus acquire a comfortable margin of strength for an occasional overload, which may be termed the acquired functional reserve.

The usual anatomic division of renal tissue into symmetrical and equal halves and the frequency of unilateral injury signalize the surgical importance of renal reserve. Excretory work and renal supply ordinarily balance. The former considered as a whole is fairly constant, but alterations in the supply produced by disease, injury or operation are frequent, and the anatomic subdivision of the renal mass accentuates these changes. The anatomic counterbalance may be relative. Complete destruction on one side has not occurred. Changes in the supply of renal tissue on one side, therefore, will either diminish or increase the demand on the other as well as on itself, since they will both have blood similarly loaded with excretory substances. In the process of establishing a new counterbalance of renal tissue on the right and left sides as a result of this alteration, there will be relative activity and inactivity in accordance to the relative reserve strengths of each.

When the right and left kidneys have a reserve power or ability to respond that is relatively similar qualitatively, they will undergo pro-

TABLE 9.—*Experiments on Repair Hydronephrosis*

Serial No	Animal	Experiment	Date of Ureteral Obstruction (Left) 1	Date of Hydroureterocystoneostomy (Left) 2	Duration of Hydronephrosis (Left) 3	Date of Nephrectomy (Right) 4	Date of Opposite Ureteral Obstruction (Right) 5	Repair Period Interval Between 2 and 4 or 5	Duration After 4 or 5	Result	Comment
Group I. With Opposite Nephrectomy or Ureteral Obstruction											
1	Cat	17-1	8/ 3/17	8/15/17	12 days	8/15/17	.....	10 days	120 days	Died; dysentery	Reparation
2	Cat	17-3	8/22/17	9/ 5/17	14 days	.....	.....	None	20 days	Died, 9/25/17	Acute pyelonephritis
3	Cat	17-17	10/10/17	10/26/17 (right, 11/10/17)	(Right, 14 days)	.....	10/26/17	.....	5 days	Died, 11/ 5/17	
4	Cat	17-15	10/ 6/17	10/24/17	17 days	.....	10/24/17	None	3 days	Died, 10/27/17	
5	Cat	17-20	10/17/17	11/ 7/17	21 days	.....	11/ 7/17	None	5 days	Died, 11/12/17	
6	Cat	17-13	10/ 6/17	10/26/17	21 days	.....	10/26/17	None	1 day	Died, 10/27/17	
7	Cat	17-11	9/26/17	10/17/17	21 days	.....	.....	.....	.....	Died under ether 10/17/17	Pyonephrosis
8	Cat	17-19	10/17/17	11/10/17	24 days	.....	11/10/17	None	2 days	Died, 11/12/17	
9	Cat	17-16	10/10/17	11/ 9/17	30 days	.....	11/ 9/17	None	5 days	Died, 11/13/17	
10	Cat	17-8	9/19/17	10/24/17	35 days	.....	10/24/17	None	2 days	Died, 10/26/17; peritonitis	
11	Cat	17-14	10/ 6/17	11/ 9/17	35 days	.....	11/ 9/17	None	5 days	Died, 11/13/17	
12	Cat	17-5	9/12/17	10/17/17	35 days	.....	10/17/17	None	8 days	Died, 10/25/17; peritonitis	Acute septic infarction; acute pyelonephritis; faulty transplant
13	Cat	17-9	9/19/17	11/ 7/17	49 days	.....	11/ 7/17	None	2 days	.....	Weight, 9.8 gm.; weight, 7.2 gm.
14	Cat	17-4	9/ 8/17	11/17/17	56 days	.....	11/17/17	None	3 days	Died, 11/10/17	Large weight, 9.4 gm.; small weight, 6.5 gm.
15	Dog	17-63	11/14/17	12/28/17	44 days	.....	2/ 9/18	42 days	2 days	Died, 2/11/18	Left kidney small and atrophic; diffuse pyelonephritis
16	Dog	17-66	11/ 6/17	1/16/17	56 days	2/26/18*	.....	40 days	16 days	Died, 3/15/18	Left kidney shrunken and ureteral transplantation to bladder in good condition; good repair nodule at each pole
Group II. Early Repair Period, When the Opposite Kidney Is Undisturbed											
1	Rat	17-22	.....	.....	10 days	.....	.....	None	.....	Died	Ether at operation
2	Rat	17-27	.....	.....	14 days	.....	.....	210 days	.....	Killed	
3	Rat	17-28	.....	.....	14 days	.....	.....	None	.....	Died	Ether at operation
4	Rat	17-25	.....	.....	21 days	.....	.....	143 days	.....	Killed	Figure 17

5	Rat	17-24	.....	.....	30 days	.....	.....	1 day	.....	Died	
6	Rat	17-9	.....	.....	30 days	.....	.....	None	.....	Died	
7	Rat	17-29	.....	.....	30 days	.....	.....	34 days	.....	Died	
8	Rat	17-12	.....	.....	45 days	.....	.....	1 day	.....	Died	
9	Rat	17-15	.....	.....	45 days	.....	.....	1 day	.....	Died	
10	Rat	17-17	.....	.....	45 days	.....	.....	Rat lost	.....	.....	
11	Rat	17-20	.....	.....	45 days	.....	.....	162 days	.....	Killed	
12	Rat	17-16	.....	.....	60 days	.....	.....	165 days	.....	Died	Figure 17
13	Rat	17-13	.....	.....	60 days	.....	.....	119 days	.....	Killed; stained intra vitam	Figure 17
14	Rat	17-19	.....	.....	95 days	.....	.....	120 days	.....	Killed	
15	Rat	17-18	.....	.....	99 days	.....	.....	2 days	.....	Died	
16	Rat	17-6	.....	.....	120 days	.....	.....	114 days	.....	Killed; stained intra vitam	
17	Rat	17-11	.....	.....	120 days	.....	.....	95 days	.....	Killed; stained intra vitam	
18	Dog	21-83	.....	.....	7 days	.....	.....	24 days	.....	Killed	
19	Dog	23-1	.....	.....	13 days	.....	.....	3 days	.....	.....	
20	Dog	21-127	.....	.....	14 days	.....	.....	26 days	.....	.....	
21	Dog	21-85	.....	.....	22 days	.....	.....	24 days	.....	.....	
22	Dog	22-24	.....	.....	28 days	.....	.....	22 days	.....	.....	Figure 16
23	Dog	17-20	.....	.....	30 days	.....	.....	1 day	.....	.....	
24	Dog	17-63	.....	.....	44 days	.....	.....	44 days	.....	.....	
25	Dog	17-66	.....	.....	60 days	.....	.....	55 days	.....	.....	Figure 18
26	Dog	17-22	.....	.....	60 days	.....	.....	100 days	.....	.....	
27	Dog	17-17	.....	.....	90 days	.....	.....	90 days	.....	.....	
					Group III. Late Repair Period, When the Opposite Kidney is Undisturbed						
1	Dog	22-22	.....	.....	7 days	.....	.....	240 days	.....	Killed	
2	Dog	21-128	.....	.....	21 days	.....	.....	249 days	.....	Killed	Figure 19
3	Dog	17-179	.....	.....	30 days	.....	.....	297 days	.....	Killed, 6/5/18	Right nephrectomy 5/28/18; nodule at each pole
4	Dog	17-56	.....	.....	45 days	.....	.....	390 days	.....	Killed, 7/18/18	Transplant right to rectum, 7/9/18
5	Dog	17-64	.....	.....	108 days	.....	.....	411 days	.....	Died, 5/ 7/17	Transplant right to rectum, 5/14/17
6	Dog	17-13	.....	.....	Partial 188 days	.....	.....	210 days	.....	Died, 9/11/18	Transplant right to rectum, 9/6/18
					Group IV. Condition of Repair in Late Period When Opposite Kidney Is Gradually Destroyed by Partial Ureteral Obstruction						
1	Dog	21-39	.....	.....	31 days	.....	.....	338 days	.....	Killed	Figure 20

[a] Transplanted ureter into duodenum.

portional changes in the process of anatomic counterbalance, even though the respective renal masses are quantitatively disproportional. The reapportionment of functional activity after the alteration occurs by a cooperative type of anatomic compensation.

When right and left kidneys have a dissimilar reserve power and an unequal potential strength, inequality of response renders counterbalance also disproportional, and that side or portion with the bigger and healthier reserve will show the greater compensation, the weaker or inhibited side gaining little or nothing in functional strength or anatomic growth by reason of the increased demand. The healthier side will gradually undergo a compensatory hypertrophy which may be so capable of counterbalance as to render the work of its weak assistant unnecessary, disuse atrophy of which will progressively occur. The reapportionment of functional activity after the alteration occurs by a competitive type of anatomic compensation.

PART II. CLINICAL STUDY

SECTION I. THE CLINICAL PRINCIPLES OF RENAL COUNTERBALANCE

1. INTRODUCTION

Renal injury of any kind is occasion for anatomic readjustment and many opportunities for a clinical study of the process of renal counterbalance in such situations are available. Functional and structural conditions are present clinically just as they are experimentally, and the pathologic change and condition are just as fundamentally more important than the functional in one as the other. There can be no permanent functional repair without an anatomic basis. The character of the anatomic equipment forms the scaffolding on which functional efficiency or inefficiency is built. The clinician is greatly handicapped because he gets only a distant view of the structure. He cannot enter to study its rooms, their arrangement, and the way they are used. A study of the garbage forms about his closest contact.. Understanding, therefore, has grown slowly and by purely empiric means. Functional values are recognized indirectly by reason of comparative tests, not by actual and exact measurements.

In the clinical application of considerations of renal reserve and competition, of renal hypertrophy and of renal atrophy, one is confronted at once with the limitation and inadequacy of functional tests, above all their failure to give any degree of accuracy in the estimation of anatomic conditions. Many medical men have come to the point even of discrediting the value of any attempt at correlation and prefer a strictly clinical classification of nephritis, and renal surgeons have come to recognize that the findings of relative function are of little value as a

guide to prognosis of surgical conditions compared to other urologic findings—the microscopic study of the separate urines, character of flow, pelvic capacity and pyelography, etc. There is a remarkable parallelism in the results of all tests which tends also to minimize their usefulness. Nevertheless, the study of renal function in all medical and surgical conditions of the kidney is invaluable, and the very limitations of the tests with which we are familiar only emphasize the necessity of persistence in an effort to perfect and to understand them better. New and more satisfactory tests may be expected to follow on the heels of a better understanding of the mechanism of renal activity, search into which has received renewed impetus in recent years largely by reason of the unsatisfactory nature of these functional studies.

2. RENAL FUNCTION AND FUNCTIONAL TESTS

1. *Dual Character of Renal Work.*—The perfection of tests of function, discovery of new tests and the more accurate interpretation of known tests cannot progress in advance of an understanding of function itself. There is as yet no theory of the mechanism of renal activity that is entirely satisfactory. A complete explanation in all details is wanting. The kidney is more generally than formerly regarded as something more than essentially an organ for the elimination of waste products. Realization of another, and in some ways more important, activity grows certain with the slow accumulation of facts; of an activity that regulates the optimum reaction of body fluids, retaining alkali and eliminating the excess of acids, which may amount to the equivalent of from 3 to 3.5 gm. of pure sulphuric acid in a day (Maclean [123]). Blood plasma through its buffer system and the assistance of the lungs and kidneys is maintained at a practically constant and faintly alkaline reaction, while normal urine is distinctly acid or temporarily strongly alkaline.

> From the constant slightly alkaline plasma, a urine is extracted which, compared with the plasma, may have in one hour a considerable alkalinity and in another hour an even more marked acid reaction. The interesting point here is that when the urine is formed we have a change from the buffer system of the blood, the bicarbonate-carbon-dioxid system, to a quite new buffer system of the urine, the phosphate mixture system (Berglund [124]).

The lungs get rid of the excess carbon dioxid and the bowel of some of the phosphoric acid. But the acid excreting function of the kidney is not simply one of elimination. The kidney attempts to retain the basic part of the acid radical. It acts to regulate the retention of the inorganic salts and water at an optimum equilibrium so that tissues and cells will

123. Maclean, Hugh: Modern Methods in the Diagnosis and Treatment of Renal Disease, Philadelphia, Lea and Febiger, 1922.

124. Berglund, H.: Nitrogen Retention in Chronic Interstitial Nephritis and Its Significance, J. A. M. A. **79**:1375 (Oct. 21) 1922.

be bathed in a physiologic medium. The threshold balance of chlorin, phosphorus, sulphur, magnesium, calcium, potassium and sodium in the blood is as important a function as their elimination and that of waste nitrogen. The kidney serves two purposes: the one is the removal of waste products, the other is the maintenance of a chemical equilibrium in the blood by removing or retaining certain substances up to a more or less fixed balance.

2. *Mechanism of Renal Activity in Light of Recent Experimental Work.*—It may be well briefly to review some of the more recent studies relative to the mechanism of this dual function. The structural differences of the renal tubule, and its unusual blood supply, strongly indicate, as has been emphasized, a separate purpose for each of its four portions, but the necessity of close cooperation between them is evident if for no other reason than because of the marked circulatory and form unity. Renal structure forms the chief foundation of most theories of renal activity, and for this very reason most theories are incomplete because all structural peculiarities are not considered.

The admirable summary of all experimental facts up to 1917 by Cushny [125] and his elaboration from this material of the so-called modern theory of urinary excretion as a combination of glomerular filtration and tubular reabsorption is familiar to all. The purely physical process of filtration in the glomerulus is coordinated, by structural conditions and common blood supply, with a tubular mechanism of an entirely different nature, dependent on the vital activity of the epithelium but by no means free of physical forces. The physical process of filtration, for example, is governed by such factors as a difference of pressure on the two sides of the membrane; variations in the permeability of the glomerular membrane and changes in osmotic resistance of the plasma colloids. The vital process of absorption in the tubules, on the other hand, is governed by such factors as variations in the absorbing power of the cells, such as may be produced by the action of certain chemical substances, phlorhizin for example; variations in the osmotic resistance of the fluid passing through the tubules, and variations in the rate of tubular flow. For a detailed discussion of these factors and a consideration of the experimental evidence up to 1917, in their support or otherwise, Cushny's [125] monograph is available. His explanation has not been accepted as a proved hypothesis. Contributions of merit have since appeared, some of which support the idea that processes of filtration and absorption are active in the formation of the urine, but others of which as strongly support the view

125. Cushny, A. R.: The Secretion of the Urine, New York, Longmans, Green & Co., 1917.

that an active secretion, in part at least, of some substances, and even the more vital process of synthesis of certain others, is performed by renal cells.

Particularly significant are the original and convincing researches of Richards [126] into the relative importance of blood pressure and blood flow to urine formation, a field of active dissension from earliest times to the present. When the rabbit's kidney is perfused in situ with whole hirudinized rabbit's blood by a method (Richards and Drinker [127]) which permits the pressure within the renal circulation to be altered without altering the total blood flow or volume output of the organ, changes of an increase in perfusion pressure induced by splanchnic stimulation or by stimulation of the medulla, by introduction of epinephrin or nitroglycerin and by partial compression of the renal vein produce parallel changes of an increase in the rate of urine elimination. These are results which are believed by the experimenters "to constitute direct evidence in support of the filtration hypothesis of glomerular function" (Richards and Plant [128]).

In another series of experiments, it was found that the changes induced by epinephrin may vary with the amount used, injection of minute doses producing a rise in perfusion pressure even though the blood flow through the kidney remains constant or even decreased, and always accompanied by an increased output of urine. This unusual type of diuresis, with diminished blood flow, is explained as an effect of specific action (contraction) on the efferent vessels of glomeruli, narrowing of which without narrowing of the afferent branch would cause an increase of intraglomerular pressure and a distention of the malpighian bodies, thus accounting for the rise in perfusion pressure (dog, rabbit and cat) and the swelling of the kidney (dog and rabbit). (Failure to note swelling of the cat's kidney is possibly accounted for by the peculiar venous system of the kidney of the cat, the external system of veins of which act as a capsule to prevent expansion [Fig. 9]. Its effect on the degree of dilatation in hydronephrosis is shown in Figure 24, an eighteen months period of complete ureteral obstruction. This should be compared with Figure 25, the same period of obstruction in a dog.) This simple explanation of an increased flow of urine with diminished blood flow through the kidney after epinephrin, as being due to contraction of efferent capillaries independently of the other blood vessels of the kidney, is of great physiologic significance,

126. Richards, A. N.: Kidney Function, Am. J. M. Sc. **163**:1-19 (Jan.) 1922.

127. Richards and Drinker: An Apparatus for the Perfusion of Isolated Organs, J. Pharmacol. & Exper. Therap. **7**:467-483, 1915.

128. Richards, A. N., and Plant, O. H.: Urine Formation in the Perfused Kidney: The Influence of Alterations in Renal Blood Pressure on the Amount and Composition of Urine, Am. J. Physiol. **59**:144-183 (Feb.) 1922.

and has a direct bearing on another matter of dispute for many years—the nervous control of the kidneys.

Marshall and Kolls,[129] after a careful study of this problem, were unable to show, just as many others before them have failed to do, that the renal nerves convey any secretory fibers to the kidney, although numerous vasoconstrictors and a few vasodilators exist. But in spite of failure earlier to establish secretory nerve fibers for the kidney, Marshall [130] in collaboration with Vickers more recently presented experimental proof of tubular secretion for phenolsulphonephthalein (discussed later). It has long been known that a few fibers of the vagus go to the kidney, but their relation to function is unknown. The details of the mechanism of sympathetic fibers in relation to urine formation are also unknown, but speculation as to variations in constriction and dilatation of different afferent and efferent vessels, and even of the venules, is interesting. Krogh,[131] Carrier [132] and others demonstrated (Lombard's method; drop of glycerin, illumination with Nernst lamp, examination with Greenough's binocular) that the capillaries of the body can and do contract and dilate independently of arterial pressure and in response to local and general stimulation so that nervous control of the kidney need be of secondary importance only. Physiologists have also called attention to the fact that the caliber of capillaries may be altered by substances in the blood as it flows through them and without the intervention apparently of vasoconstrictor and vasodilator nerve fibers. Epinephrin and pituitary extract are given as examples, and the regulating action of certain definite substances in the blood may be a prominent characteristic of the kidney whose afferent and efferent vessels must have blood of considerable difference in composition. Still another regulating factor in vascular dilatation and constriction is the purely mechanical one of internal pressure which may act as a stimulus to increase the vascular tone. Simple distention of the vessel may react to maintain the normal tone. Such considerations offer some understanding of the continued normal activity after complete renal enervation.

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129. Marshall, E. K., Jr., and Kolls, A. C.: Studies of the Nervous Control of the Kidney in Relation to Diuresis and Urinary Secretion, Am J. Physiol. **49**:302-325 (July) 1919.

130. Marshall, E. K., Jr., and Vickers, J. L.: Mechanism of Elimination of Phenolsulphonephthalein by Kidney Proof of Secretion by Convoluted Tubules, Bull. Johns Hopkins Hosp. **34**:1-7 (Jan.) 1923.

131. Krogh, A.: The Number and Distribution of Capillaries in Muscles with Calculations of the Oxygen Pressure Head Necessary for Supplying the Tissue, J. Physiol. **52**:409-415 (May) 1919.

132. Carrier, E. B.: Studies on the Physiology of Capillaries, V, The Reaction of the Human Skin Capillaries to Drugs and Other Stimuli, Am. J. Physiol. **61**:528-547 (Aug.) 1922.

It has been a general observation that stimulation of the splanchnic, by vasoconstriction, reduces urine formation, but that section of the nerve, by vasodilatation, increases it. Marshall and Kolls [129] found that section of the splanchnic on one side produced a unilateral diuresis typical of sodium chlorid diuresis which persisted for months (though, in Quimby's [133] experiments, recovery was noted by him in from ten to fourteen days). This diuresis is probably due to an increase in blood flow. It may be caused to disappear by the administration of nicotin, which paralyzes the sympathetic ganglion cells.[129] It is curious to note that, after ligation of the anterior or posterior branch of one renal artery, which reduces more or less uniformly the urinary function by half (recent experiments in collaboration with Dr. Butler [30] lead us to question this statement of a 50 per cent. reduction in function [Part I,

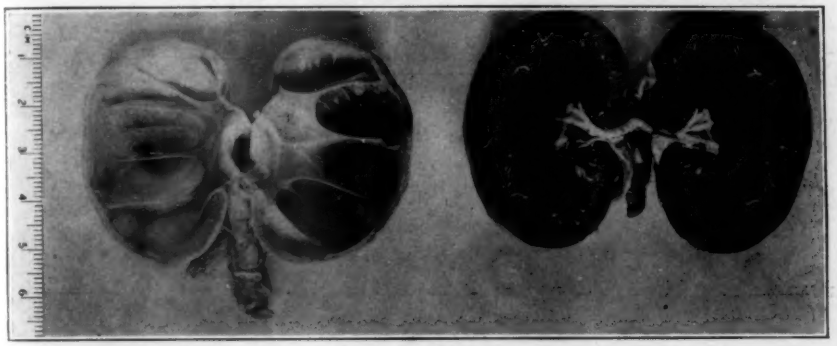

Fig. 24.—Eighteen months simple hydronephrosis in a cat which shows complete hydronephrotic atrophy without dilatation, the hydronephrotic kidney not being any larger than its hypertrophic fellow. Failure of dilatation is due to the peculiar type of superficial venous system of the cat's kidney (Fig. 9). Comparison should be made with the eighteen months hydronephrosis in a dog shown in Figure 25.

Section I, and Figure 2]) section of the splanchnic may now cause this kidney to eliminate more water and chlorids than the other intact kidney, while creatinin and phenolsulphonephthalein will remain relatively as before, and urea will stand in an intermediate position. The increased blood flow and consequent diuresis has not affected creatinin and phenolsulphonephthalein and only slightly the urea output. These findings are significant in connection with the more recent studies of Marshall and Vickers,[130] which they regard as proof of the secretion of phenolsulphonephthalein by the convoluted tubules, and which may explain the failure of an increase of phenolsulphonephthalein and

133. Quimby, W. C.: The Function of the Kidney When Deprived of Its Nerves, J. Exper. Med. **13**:535-548 (April) 1916.

creatinin in their "50 per cent. kidney" with unilateral diuresis, as splanchnotomy has had no effect on the secretory epithelium. The proof of tubular secretion presented by them lies in the reputed accumulation of phenolsulphonephthalein in the cells of the convoluted tubules after blood pressure had been lowered so as to eliminate the possibility of glomerular filtration. They find that, after intravenous injection, phenolsulphonephthalein is present as a free substance, filterable, and a bound one, nondiffusible. The free phenolsulphonephthalein passes through with the glomerular filtrate, the bound, and in the case of cessation of filtration with low blood pressure, the free phenolsulphonephthalein also is absorbed into the epithelial cells of the convoluted tubules and this store of phenolsulphonephthalein is gradually eliminated later. The amount of bound and nondiffusible phenolsulphonephthalein in the plasma, they find, differs with species, from 60 to 75 per cent. of it being in this form in dog's plasma, while in the rabbit from 95 to 98 per cent. of it is in this condition.[130] According to this conception, phenolsulphonephthalein, in the rabbit, is almost wholly a test of tubular secretion, whereas in man, in whose blood 34 per cent. of the phenolsulphonephthalein is bound, the test is only one third tubular. How much of the free phenolsulphonephthalein normally is bound in the tubules, however, is unknown.

A third set of experiments on the regulation of renal activity with urea as a guide (Addis[134] and co-workers) is well worthy of careful consideration. In the first place, these workers have been unable to verify Ambard's[26] mathematical laws and formulas regarding the rate of urea excretion as predicted from any observed concentration of urea in the blood or urine, and regard Ambard's constant as insecure and inaccurate. Furthermore, these authors also are inclined to regard the tubular epithelium as secretory, in part at least, and not wholly absorptive.

The simple ratio of the urea concentration in one hour's time, as a measure of work done, to the urea concentration in 100 c.c. of blood, as a measure of work required, gives a better approximation of the quantity of actively functioning kidney tissue than does Ambard's constant or other urea tests. For example, the average rate of urea excretion after the administration of a known amount is roughly a measure of the size of the kidney. Comparison of the ratios following urea administration before and after removal of one kidney, in the rabbit, for example, gave an average of from 1.29 to 0.54, or less

134. Addis, T., and Co-workers: The Ratio Between the Urea Content of the Urine and of the Blood After the Administration of Large Quantities of Urea. J. Urol. **1**:263-287 (June) 1917.

than half when only one kidney remained (Addis [135] and Watanabe), and a study of the average rates of urea excretion in the rabbit as compared to man showed the latter to be approximately thirty times greater. Since the renal tissue of man is about thirty times that of the rabbit, it follows that the order of magnitude of the average rate of urea excretion is relative to the size of the kidneys (Addis, Shevky and Bevier [136]). These fundamental studies give additional emphasis to the value of urea determinations in the estimation of renal function. Consideration of further studies of Addis [135] on the regulation of urea excretion by epinephrin and pituitary extract are particularly interesting in connection with the results of Richards [126] and of Marshall.[137] Epinephrin increases the rate of urea excretion even in spite of a lowering of the blood urea concentration, and there is an optimal subcutaneous dose for this augmenting effect (Addis, Barnett and Shevky [138]). Pituitary extract, in effective doses, is followed by a decrease in the urea excreting activity of the rabbit's kidney, and this rate is lower than in animals not given pituitary extract, even though the blood urea concentration is higher.[138] A kidney under strain in excreting large amounts of urea (high blood urea) shows less response to epinephrin and pituitary extract than a normal kidney (Addis, Foster and Barnett [139]), and under physiologic conditions epinephrin and pituitary extract are found to be mutually antagonistic; each will neutralize the effect of the other.[136] The activity of the kidney in excreting urea is thus seen to depend on two main factors, "a fixed and mechanical regulation through the urea concentration in the blood and another and overruling type of regulation which acts through the central nervous system."

Richards,[126] in watching glomeruli of the frog's kidney function under the binocular microscope, has demonstrated marked variability in the activity of each glomerulus and considerable irregularity in the work of different ones at any one time, even though they all have blood of the same composition and pressure. The vasomotor or chemical mechanism controlling the constriction and relaxation of afferent and

135. Addis, T.: A Method of Measurement of the Urea Excreting Function of the Kidneys, J. Biol. Chem. **28**:251 (Dec.) 1916.

136. Addis, T.; Shevky, A. E., and Bevier, G.: The Balance Between the Regulation by Adrenalin and by Pituitrin, Am. J. Physiol. **46**:129-146 (April) 1918.

137. Marshall, E. K., Jr.: A Rapid Clinical Method for the Estimation of Urea in Urine, J. Biol. Chem. **14**:283-290, 1912-1913; footnote 129.

138. Addis, T.; Barnett, G. D., and Shevky, A. E.: The Regulation of Urea Excretion by Adrenalin, Am. J. Physiol. **46**:39 (April) 1918.

139. Addis, T.; Foster, M. G., and Barnett, G. D.: The Effect of Adrenalin and Pituitrin on the Action of the Kidney Under Strain, Am. J. Physiol. **46**:84-89 (May) 1918.

efferent vessels is apparently of very great importance and not even under group control. It is individualistic rather than communistic. Blood corpuscles, in a Richard's [126] frog preparation, as we have observed in confirmation, may be seen to stream in a regular flood through the capillaries of one glomerulus while those of another right alongside are empty, but in the next minute, these collapsed capillaries of a glomerulus may open up and transmit a rapid file of corpuscles while those of its neighbor, so active a moment before, gradually empty and fade away, a corpuscle often hanging suspended at the entrance of its afferent vessel before being carried off in the stream of a side branch. It would seem, therefore, that the units do not always work to their limit of capability and that, while an increase of total activity occasions the bringing into activity of a proportionally greater number of units, the units themselves also can contribute to total function by an increase of the degree of their activity. The frequent dual and triple vascular arrangement of the individual glomerulus is in itself an anatomic basis for this individual variability (Fig. 3).

From analogy it is safe to reason that tubules act similarly to glomeruli in an intermittent manner. The inactivity of a glomerulus shuts off blood to that tubular portion supplied by the capillary tufts of its efferent vessel and diminishes the tubular flow of its own tubule. Possibly there is an overlapping or interdigitation of the capillary beds of the convoluted tubular areas so that the constriction of the efferent vessel or a rest period of the glomerulus itself will fail to shut off the blood supply of that respective tubular cap in view of an overlapping supply from another glomerulus. The rest periods of each glomerulus, however, must influence the amount and rate of flow of its own tubular contents and thus have an indirect effect on its own tubule.

The relation of structure to function, so frequently mentioned, if true, precludes the acceptance of any theory that so far has been advanced. No one gives the final and complete explanation of renal activity. Maclean [140] cannot accept Cushny's [125] explanation in toto, raising objections by reason of this theory's failure to apply in certain pathologic conditions, in which there would have to be a selective secretory activity on the part of the glomerular epithelium to explain the blood and urine findings. Stieglitz [141] revives Heidenhain's [142] argument (1874) for tubular secretion by concluding "that

140. Maclean (Footnote 120, p. 5).

141. Stieglitz, E. J.: Histochemical Studies on the Mechanism of Renal Secretion, Am. J. Anat. **29**:33-89, 1921.

142. Heidenhain: Arch. f. mik. Anat. **10**:1, 1874; Handbuch der Physiologie (Herman) **5**; Arch. f. d. ges. Physiol. **9**:1; 335.

the route of iron secretion is through the cells of the convoluted tubules," and Marshall and Vickers [130] advocate the same route for phenolsulphonephthalein. Addis,[135] as has been stated, is not prepared to abandon the idea of a tubular secretion, at least for certain substances, and urea particularly, and even Cushny,[125] in his preface, clearly states that "finality in our ideas of the mechanism of urinary secretion has not yet been attained." When one considers the absolute uniformity and complex perfection of kidney structure, the tubular unit and its four portions, the end arterial system and double capillary system of blood supply to the glomeruli and tubules, the two distinct efferent types of vessels from glomeruli, one to convoluted, the other to Henle loops, and the remarkably clear-cut zones that are formed as a result of this uniform arrangement, one cannot escape the necessity of finding that it is purposeful. There must be coordinated activity. And when one tries to reconcile experimental and clinical studies with anatomic structure, it is seen that we are far from being fully conversant with the exact mechanism of renal function and of its dual activity. Experimental and clinical studies indicate, at this time, that it is a combination and coordination of filtration, absorption and secretion, and possibly, from the studies of Benedict,[143] also of synthesis (hippuric acid, creatinin and ammonia), but of the exact details of this activity we remain in ignorance. A most encouraging advance is in progress, but the true explanation, it is safe to say, will not be a simple one.

Standardization of functional tests to specific values is impossible in the light of this continued ignorance of normal function, and particularly significant is the nearly parallel nature of the information given by all known tests of renal function. An exact interpretation of their meaning is not always possible. Their great empiricism renders control of all errors essential but difficult. For this reason, the simplest tests are safest. The greatest of all difficulties in their application and interpretation lies in the variable influence of renal inhibition.

3. *Renal Inhibition.*—Varying periods of activity and inactivity have been demonstrated for individual units as well as whole portions of the kidneys. The variability in the work of two perfectly normal kidneys, when measured for short periods, is often pronounced; as early demonstrated by Albarran,[144] there may be as much as 30 per

143. Benedict, S. R., and Nash, T. P., Jr.: The Ammonia Content of the Blood, and Its Bearing on the Mechanism of Acid Neutralization in the Animal Organism, J. Biol. Chem. **48**:463 (Oct.) 1921. Behre, J. A., and Benedict, S. R.: Studies in Creatinin and Creatinin Metabolism, J. Biol. Chem. **52**:11 (May) 1922.

144. Albarran, J.: Etude sur le rein des urinaires, Thése, Paris, **184**:4 1889; ibid., **195**:4, 1889.

cent. difference in an hour's time between the work of one and the other. Failure of equal and uniform effort when in perfect health on the part of portions as well as of the individual units of each complicates matters when one or both become diseased. Each kidney with respect to its mate and each individual glomerulotubular unit with respect to others in its own or distant neighborhood may show variable rest periods and variable degrees of activity. These differences are for short periods and are equalized in the course of a day so that each kidney and probably each unit thereof does an equal share of the total work.

But there may be, as a further complication to functional study, an abnormal degree of activity of both kidneys, or of one kidney as a whole, or of the individual portions, unrelated to injury or disease; these abnormal functional variations are recognized as types of functional inhibition and of hyperactivity or hyperpermeability. The intricacy of the mechanism of renal activity, in all its phases, is sufficient warranty for a multitude of factors as cause for renal inhibition. The inhibition of renal activity following ureteral catheterization is a well known example. A so-called reflex anuria of one or both kidneys may follow catheterization and persist for many hours or just the opposite conditions of a pronounced polyuria, with failure in the ability of one or both kidneys to concentrate may develop (Kapsammer,[121] Keyes and Stevens[122]). These possibilities render the interpretation of results of functional study extremely hazardous at all times and constitute a marked limitation to their value.

Clinically, three types of renal inhibition may be recognized: (1) reflex, (2) pressure, and (3) chemical, or toxic. Reflex inhibition is the most familiar of all. The ureteral reflex which follows the passage of a catheter or stone has just been referred to, but its effect may be felt by the opposite kidney as sometimes happens with unilateral disease, the renorenal reflex. The effect of one kidney on the other is manifested through common nerve connections and especially through anastomosis of the renal plexuses with the inferior mesenteric sympathetic ganglion. Bartrina[145] found that the inhibitory effect of a calculus in one kidney lowered the daily urea excretion of the opposite and apparently healthy kidney to scarcely more than 1 gm., and three days after nephrectomy the daily output of urea rose to 68 gm. Renal inhibition may be produced by vesical irritation, the vesicorenal reflex, and by cerebral irritation, the cerebrorenal reflex, following fear or excitement.

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145. Bartrina, J. M.: Genito-Urinary Reflex Phenomena, J. d'urol. méd. et chir. **13**:337-341 (May) 1922.

The functional insufficiency that follows urinary obstruction from calculus is sometimes spoken of as a pressure inhibition when function returns to normal immediately on relief of the obstruction. But the explanation is unsatisfactory when applied to the similar condition of lowered function that sometimes occurs with prostatic enlargement before the muscular compensation of ureters and ureteral orifices is broken. The reduced renal function of this condition cannot always be attributed to damage from back pressure in those cases in which ureters and pelvis yet remain unaffected. It is more likely an inhibitory type of insufficiency recovered from readily on relief of the bladder obstruction. It is possible that pressure inhibition therefore is always primarily reflex, and that disuse, anemic and pressure atrophy come secondarily. The opposite effect from partial ureteral obstruction, in which the urine exceeds that of the unobstructed side and in composition shows changes common to all forms of diuresis, has been frequently noted experimentally and occasionally described clinically. This "pressure diuresis" is probably the result of a reflex vasodilatation.

Lastly, chemical or toxic types of inhibition occur as in certain types of unilateral tuberculosis or pyonephrosis, or in general septic conditions without renal involvement.

All these reflex conditions, probably associated with reflex nervous vasoconstriction or vasodilatation, and causing inhibition or stimulation of function, have to be recognized and differentiated from a true loss of function secondary to loss of renal tissue by disease, or from an increase of renal mass by hypertrophy, and even with true functional loss from disease, there is associated often an inhibition of function which confuses and adds to the anatomic loss of function.

4. *Tests of Renal Function and Their Limitations.*—Tests of renal function have centered chiefly on that renal work concerned with the removal of waste products as measured by the amounts excreted, retained or combination studies. No test has ever been suggested to estimate tubular reabsorption nor tubular secretion, and there is no specific test of the function pertaining to the regulation of a chemical equilibrium. When it comes to practical use, the real distinction between secretion, filtration and absorption seems inadvisable. Glomerular and tubular activity are too interdependent to be easily separated, of which failure to find specific tests is proof. There may be two types of absorption, one from convoluted tubules, the other from Henle's loops. Everyone, however, is beginning to realize that too little attention has been paid to the glomerulus in this copartnership. This has doubtless been due to the fact that the changes of tubules in disease are obvious, whereas marked alterations of the filtering membrane would pass unobserved. This also may account for the neglect of Henle's loop in

the scheme of things. The marked parallelism of all tests of renal function in the face of renal insufficiency might signify something in regard to the fundamental importance of the glomerulus in all renal work. Specific tests must follow and not precede determination of specific activity.

The methods used in the estimation of this functional work of the kidney are of three types: (*a*) Tests of excretion; (*b*) tests of retention, and (*c*) combination tests.

(*a*) Tests of Excretion: Tests of excretion, such as the polyuria test of Albarran,[144] diastase, phlorhizin, sodium iodid, lactose and dyestuffs (indigo-carmin, phenolsulphonephthalein, etc.,), give an estimation of the speed and ability of kidneys to remove substances from the blood and pass them into the urine. Their value is empiric. The functional power of normal kidneys, as averaged from many control tests, forms the criterion. Anything short of this means insufficiency. This may not be actual, in an anatomic sense, but purely temporary from functional inhibition, which, as already intimated, may have a multitude of causes. The test may even show a normal output when renal tissue is far from normal as in so-called hyperpermeability. Excretion tests, at their best, only show what the kidney can do in this limited line of excretory work for this particular period, and they give no direct information of what the kidney has been doing or is capable of doing. The information furnished by all of these tests, furthermore, is almost identical in nature. The idea that one tests somewhat glomerular and another tubular activity is no longer tenable. Some may be more valuable than others, but, if so, their greater value hangs on technical advantages rather than on points of interpretation. Phenolsulphonephthalein surpasses all the others in such advantages, and a growing realization of this has led to its almost universal adoption as a test of excretion. The information furnished by it is of no greater significance than that of many of the others, but the simplicity and accuracy of the test make such information more reliable.

(*b*) Tests of Retention: Tests of retention indicate renal insufficiency when substances normally excreted accumulate in the blood above a normal concentration. Such retention through inability of renal activity may be only temporary as in the anuria of calculus, and a measure of it is in no way a test of renal reserve or hypertrophy. With minor exceptions all tests of retention have identical significance. Sometimes retention of chlorids (chloruremie of the French) predominates over retention of nitrogen (azotemie) or vice versa, and the accumulation of creatinin does not always progress in direct proportion to urea.

The acid fixing power of the blood, the alkali reserve of the plasma and of the blood bicarbonate, has recently come into use as a test of

renal function on the assumption that the kidney regulates the acid or alkaline content of the body fluids, and disturbance of this activity will be indicated by an alteration in the normally constant acid or alkali binding power of the blood. The simplest test of acidosis is that suggested by Sellards,[146] testing the reaction of the urine after giving definite amounts of sodium bicarbonate by mouth. Rieger and Freund [147] measure "oxydesis" by estimating the greatest amount of acid that may be added to a unit volume of whole blood without agglutinating its erythrocytes, and find it increased early in the diffuse but not changed or decreased until the later stages of degenerative vascular nephropathies.

But, in general, there is a very limited latitude for interpretation of differences of significance between all tests of retention, just the same as in all tests of excretion, and, in this respect, one test is just about as rich in information as another. Urea is regarded as the equal of any and its greater simplicity of estimation makes it preferable. None give any indication of what the kidney has done or may do any more than do tests of excretion.

(*c*) Combination Tests: A combination of one or more tests of excretion with one or more tests of retention in the study of renal function has been found to be of advantage in certain conditions. As a rule, the findings of excretion tests and retention tests also parallel each other remarkably. Tests of excretion, however, show changes in acute lesions earlier than tests of retention, because the accumulation of substances in the blood to the point at which they become significant requires times. Excretion tests (phenolsulphonephthalein), for the same reason, indicate insufficiency in the milder lesions in advance of retention (blood urea), so that, when normal, there is no object in testing retention. But when phenolsulphonephthalein is low, retention tests have considerable value in indicating more exactly the degree of this insufficiency. A low phenolsulphonephthalein without retention of urea in the blood indicates a lesser degree of insufficiency than a low phenolsulphonephthalein with urea retention, and the amount of retention is a further guide of the degree of insufficiency.

A study of the interrelationship of the amount of urea in the blood and urine at any particular period has been found of value as a test, and Ambard,[26] and later Maclean,[123] have drawn up a set of laws governing it. The information obtained is in no way better or different from that of phenolsulphonephthalein, and because of this parallelism and the fact

146. Sellards, A. W.: The Principles of Acidosis and Clinical Methods for Its Study, Harvard University Press, 1917.

147. Rieger, J. B., and Freund, H. A.: The Alkalimetry of Whole Blood: The Acid Fixing Power of the Blood in Renal Disease, Arch. Int. Med. **30**:517-530 (Oct.) 1922.

that phenolsulphonephthalein is free of the many technical errors to which an estimation of Ambard's constant is liable, the preference of the simpler test has become almost universal. Furthermore, recent work of Addis [135] disproves the accuracy of many of these so-called laws.

Combination tests that subject renal tissue to an overload theoretically are of greater prognostic value than these other tests, and a number of modifications of Albarran's [144] old water dilution test have been developed. Undoubtedly, these newer methods are an advance in the right direction, and their perfection will go hand in hand with the growth of our knowledge of renal work. When the Maclean,[123] Rosenthal,[148] de Wesselow,[149] Addis [135] and other urea dilution tests go counter to clinical tests, it is usually owing to ignorance of their actual significance. Urea overload, however, can be only a small measure of the multitudinous duties of the kidney. The information obtained is little, if any, different from that obtained with phenolsulphonephthalein in combination with blood nitrogen. Urea concentration tests may give a somewhat closer approximation of renal capabilities but demand accuracy in estimation and are subject to the same limitations as other tests in respect to interpretation. Fixation of specific gravity, which also is of some special significance, is best shown by such tests.

Widal and Javal [150] and other French authors have emphasized the significance of sodium chlorid as an excretion test. Added to the food, it leads to edema, and reduction of salt in the diet may cause a loss of fluid from the tissue. A chlorid concentration test requires that a salt equilibrium be first established by careful dieting, and for practical purposes such tests are unnecessary. Observations of edema and weight changes are of more clinical importance.

Experimental investigation of test substances both of excretion and retention with respect to the anatomic changes normally produced by their prolonged and maximum use, as has already been suggested, may help to solve many of the problems of functional study. It is probable that such investigations will remain barren of complete results until the development of methods for determining minute changes in the flat epithelium of the glomerular apparatus, and of Henle's loops.

5. *Clinical Application of Tests of Renal Function.*—Functional tests serve two purposes, that of total function and relative function, and the renal conditions served fall into three groups: medical diseases,

148. Rosenthal: Zur Frage der Ausscheidung von disastatischem Ferment im Urin, Deutsch. med. Wchnschr. **37**:923, 1911.

149. De Wesselow: The Urea Concentration Test, in Maclean's Diagnosis and Treatment of Renal Diseases, 1922, p. 53.

150. Widal, F., and Javal, A.: La Chloruremie et la cure de dechloruration dans le mal de Bright, J. physiol. et path. gen. **5**:1107, 1903.

surgical diseases, and renal injury from lower urinary tract obstructions. The significance of functional tests is just a little different for each group. The medical lesions are commonly bilateral, and a study of the work of one kidney relative to its partner is only exceptionally helpful. Surgical conditions, on the other hand, are frequently unilateral, and even when bilateral, information of the relative work of each is always invaluable. Insufficiency, as indicated by tests of total function, in the conditions associated with obstructions requires confirmation as it is sometimes due to technical failure in the complete collection of the specimens, and moreover this group is notable both for showing inhibitory influences of function and remarkable reparatory ability on relief of obstructions. An insight into the true functional ability can often only be reached after study of a series of tests.

In the application and interpretation of tests in any of these clinical conditions, their many limitations must be remembered. They fail to indicate the degree or absence of renal reserve and the ability of renal tissue to grow. They fail to show when growth has already occurred, or the extent of this anatomic repair; but in conjunction with clinical facts, and when taken in a series over a period of time so as to control each other and always as an adjunct of a careful clinical and urinary study, they are invaluable. The many technical and inhibitory factors are difficult to control. For this reason their greatest accuracy is found in the study of surgical conditions in which the relative value of each kidney is sought. A previous knowledge of total function enables an accurate estimation of the relative part of each kidney in this work after ureteral catheterization. But their usefulness even here is empiric and at best they constitute a poor guide to the actual anatomic conditions behind renal readjustments. As functional power has an anatomic basis, tests of function constitute, nevertheless, the principal clinical criterion of renal counterbalance.

SECTION II. RENAL COUNTERBALANCE IN MEDICAL DISEASES

There has been a definite tendency in recent years to simplify the functional study of renal disease, which is the natural outcome of a better realization of the limitations of such studies. Localization tests fail altogether, and it is fair to say that a differentiation of a glomerular or tubular lesion is not possible by any test. The following very simple classification in use by Christian [151] is based largely on clinical findings and is good evidence of the want of progress. As he himself confesses, it is a sign of continued ignorance. Four groups are used: 1. Acute

151. Christian, H. A.: Method of Examining the Nephritic Patient, New Orleans M. & S. J. **76**:487-490 (May) 1924.

nephritis. 2. Chronic nephritis; (*a*) with edema, (*b*) with hypertension, and (*c*) mixed or combined type. 3. Essential vascular hypertension, progressing into chronic nephritis. 4. Renal arteriosclerosis, progressing into chronic nephritis. The lesions of nephritis may be progressive in character just as are the infectious nephritides, or may be modified from time to time by superimposed acute attacks, or by periods of reparation, all of which changes render anatomic classification of any case of nephritis difficult.

Aschoff [152] or Vollhard's [153] anatomic classification is an effort at simplification, and recognizes three groups: 1. Inflammatory nephritis; (*a*) glomerular lesion predominating; (*b*) tubular lesions predominating. 2. Noninflammatory or degenerative lesions (nephrosis). 3. Arterial or vascular lesions (sclerosis).

Irrespective of the method of classification of cases, be it on clinical or pathologic lines, much is wanting in the study and treatment of nephritis. Occasionally, in one case the patient will get well with healing of the lesion, and another case, which is identical clinically and functionally, will progress to a fatal issue. The need of better methods of study, methods which will indicate anatomic reserve and reparatory power of renal tissue, and will differentiate between inhibitory and pathologic types of insufficiency is a vital one. Reference has already been made to the often remarkable anatomic repair by group hypertrophy that has been observed in nephritis of all types (Group Hypertrophy). Such anatomic changes explain the remarkable recovery in many apparently hopeless cases. Polycystic kidneys frequently demonstrate with how small an amount of renal tissue a person may live in apparent health, but in these kidneys less injured areas are working to the height of their ability; have undergone a maximum of group hypertrophy, and break down when a greater demand arises. It is of interest to mention the beneficial effect of morcellement in such kidneys riddled with multiple cysts (Rovsing [154]). Doubtless, relief of pressure with emptying of innumerable cysts allows renewal of blood supply and greater compensatory reparation to occur. Relief of intrarenal pressure with a similar effect of compensation has been suggested (Albarran [155]) as the more probable explanation of the action of Edebohl's operation than that the kidney circulation is improved by a new capsular blood supply.

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152. Aschoff, L.: Pathologische Anatomie, Jena, Verlag von Gustav Fischer, 1923, pp. 418-467.

153. Vollhard, F.: Ueber Wandlungen in der Nephritislehre, Wien. med. Wchnschr. **72**:430-435, 1922.

154. Rovsing, T.: Treatment of the Multilocular Renal Cyst with Multiple Punctures, Hosp.-Tid., Køhenh., **4**:105-111, 1911.

155. Albarran, J.: Perinefritis; anatomia, patologica, Rev. de cien. med., Habana, 1890, p. 253.

It is neither our purpose nor capability to discuss in detail renal readjustment in nephritis. We wish to give proper emphasis to the possibilities of repair and of anatomic readjustments. Gradual stimulation by suitable diets, in some cases, is now known to hasten repair, and is preferable to the marked limitation of food so long practiced in all such cases. By no means is nephritis always progressive and fatal. Reparation may be remarkable.

SECTION III. RENAL COUNTERBALANCE IN SURGICAL DISEASES

The problem of a counterbalance in relation to surgery includes the determination of the relative renal reserve, of the relative ability to hypertrophy of the respective renal masses and, when the surgical preservation of tissue is in point, the further determination of the probable action of competition between that kidney or portion capable of hypertrophy and the one or portion incapable of growth. Reparation of one and atrophy of the other may follow the surgical procedure. For relative functional study, those tests that put renal tissue under strain would seem to be more valuable. We lack such a test with ureteral catheterization, and have to rely on a consideration of the pathologic processes as best we can determine them, together with the functions shown. It will be seen that in renal counterbalance, with its factors of reserve and competition, we have a much broader basis for the consideration of problems of renal surgery than in relative functions alone, since actual foreknowledge of the final anatomic result is attempted.

1. VALUE OF STUDIES OF RELATIVE FUNCTION

When we undertake to apply the principles of reserve and hypertrophy, competition and atrophy, to surgical problems, the confusion between a functional and an anatomic counterbalance is irremediable in view of our inability to correlate functional findings with anatomic conditions. We have no tests of renal reserve and cannot distinguish the degree or even existence of native, compensatory or acquired reserve power. Phenolsulphonephthalein is the simplest test available for the determination of the relative abilities of two kidneys. It is the only test which gives, with any degree of accuracy, an estimation of absolute renal values. Nevertheless, with ureteral catheterization there are a number of factors that influence the test which are difficult to control. Inhibition of function, as the result of ureteral or renal irritation or other causes, has been discussed and is the most troublesome. Not infrequently a perfectly normal kidney will put out a very small amount of the dye in the thirty-minute period, and the opposite kidney may be hyperactive at the same time, giving the appearance of unilateral disease with opposite

compensatory hypertrophy. In this type of inhibition, the amount of urine secreted by the two sides is very unequal and usually the inhibited side will fail to function at all for short periods. The excretion of phenolsulphonephthalein is only inhibited when the flow of urine is scanty. A low phenolsulphonephthalein with a free flow of urine through the catheter is reliable evidence of diminished function. Peterson's [156] concentration test may be of value in cases of inhibition. The 5 c.c.. on the inhibited side would have as good or better concentration than 5 c.c. on the active side. Watching the rate of flow and knowing the total amounts for the two sides also gives reliable information. Another not infrequent type of inhibition is that in which both kidneys fail to function actively, sometimes no urine coming from either side after catheterization for considerable periods. In such a case, repetition of the test is the only recourse. Unilateral inhibition without hyperactivity of the opposite side is recognizable because of the discrepancy between the total phenolsulphonephthalein previously estimated and the total of the two sides on catheterization—a one hour's output, after intralumbar injection, approximately equals the combined ureteral output of thirty minutes after intravenous injection.

Leakage into the bladder along one or both catheters leads to error but is easier to control. The amount of phenolsulphonephthalein in the bladder at the end of the period of ureteral collection shows the amount of leakage, and whether this is all from one side, or equally or disproportionally from both, is often immaterial, if comparison of percentages actually found is unaltered by the addition to either side.. Thus, when the right is 30 per cent., the left, 5 per cent., and the leakage, 10 per cent., the addition of all the leakage to the left, still leaves it 50 per cent. deficient. Whenever this correction is not possible, a repetition of the test is required.

But even with perfect control of errors due to reflex inhibition or to leakage around catheters, the absolute values obtained with phenolsulphonephthalein are inadequate as a guide to a conservative or radical surgical procedure. The test, or any test, gives an estimation of the functional activity of each kidney for the period of the test and that only. It gives no indication of renal potentiality or reserve. Such reserve may be absent and the function shown by phenolsulphonephthalein be the maximum that the kidney is capable of, and this maximum work may be performed by renal tissue incapable of compensatory changes, as in an infantile kidney or by tissue which has already developed as great a degree of hypertrophy as is possible. What renal tissue is capable of hypertrophy is not shown by any known test.

156. Peterson, A.: Modification of Differential Functional Test with Phenolsulphonephthalein, J. Urology **7**:73-75, 1922.

The excretory ability of a kidney may also be inhibited by disease or conditions, either in itself or in its fellow, as well as by the reflex irritation of a catheter, stone, fear or excitement, and these inhibited kidneys may have considerable reserve power when the inhibiting factor is withdrawn and the proper stimulus given. Renal tests do not tell us when we are dealing with this type of inhibition. The ability to do more work on demand, or what one may term static reserve, as is thoroughly demonstrated by the foregoing experimental work, is quite limited, whereas potential reserve or the power of renal tissue to take on more work by hypertrophy may equal four times the present value. Some test that would put an overload on renal tissue might better test static reserve, but would fail to differentiate a native reserve or the reserve present in a normal kidney from an acquired reserve, which develops with compensatory hypertrophy. The development of renal hypertrophy requires time and an increase of activity, and we have no test of this potentiality.

Another difficulty in the application of renal function to surgical judgment, as has been mentioned, is the lack of correlation between function and anatomic structure. This confusion is well indicated by the foregoing discussion on renal reserve. The same functional values may be given by renal tissue that has a good and unused potential reserve, by tissue that has no reserve, and by tissue that has undergone a complete compensatory hypertrophy and has only an acquired reserve. The first only is capable of growth and able to double its present work. On the other hand, markedly diminished function may be shown by tissue capable under other conditions of normal function. It will be seen, therefore, that in a consideration of renal compensation in relation to surgery, a careful distinction between a functional and an anatomic counterbalance must be made.

With respect to functional counterbalance, we are apt to confuse the relative and total functions, and when speaking of a complete functional counterbalance mean that the total renal function has become normal. But the readjustment of the anatomic conditions on the two sides and their respective relative functions may not be completed to a permanent ratio for many months or years afterward. It is a consideration of anatomic counterbalance, rather than functional restoration, that counts for good judgment when a decision is to be made for or against a radical or conservative operation. Relative functional tests are at best good guides only. A knowledge of the actual anatomic conditions and the reserve present in each kidney is of much greater value. Often this cannot be completed before operation, and even with one kidney in our hands, we are at a loss because the actual conditions of the other are still problematic, though we may have reliable tests of its function as a

guide. In a consideration of renal counterbalance, clinically, this confusion between a functional restoration and anatomic readjustment is therefore inevitable. Nevertheless, many clinical examples of the fundamental principles involved in the process may be collected.

Renal surgery has to deal with unilateral and bilateral conditions, and each group presents distinctive problems. It is a popular rule that in bilateral disease it is safest to operate on the best kidney first, and that in unilateral disease the safest and surest cure is by nephrectomy. There are so many exceptions to such a policy that it should be forgotten and every case considered on its own individual merits. The ultimate anatomic readjustment that may be expected to follow any proposed operative procedure is a most important preoperative consideration. A knowledge of the pathologic change in each side gained by a careful and complete urologic examination usually enables fairly accurate approximation of the final result and, with a mind open to any unexpected surgical findings, makes renal surgery unusually efficient and reliable.

2. APPLICATION OF PRINCIPLES OF RENAL COUNTERBALANCE TO SURGICAL PROBLEM OF UNILATERAL DISEASE

Even though nephrectomy is usually the safest operative procedure in distinctive unilateral disease, it is by no means the wisest in all cases. In lithiasis, for instance, one can never tell when stones will form on the opposite side, which would then be the only kidney. Conservation of renal tissue should come second only to preservation of life, but it must never be forgotten that surgical preservation does not always secure permanent preservation. Sacrifice of a kidney with a large amount of active parenchyma is often required as in tumor, tuberculosis or hemorrhage, but, in stone or hydronephrosis, the proper procedure is often difficult to determine.

(*a*) *Renal Calculus.*—In cases of unilateral nephrolithiasis, the greater risk of a conservative operation must be weighed against the advantage of preservation of the kidney. Pyelotomy is the method of choice, but nephrectomy should have preference in those cases complicated by severe infection or marked renal destruction. In other cases of unilateral stone with good healthy parenchyma, but in which pyelotomy is not possible, the question arises as to how extensive a nephrotomy with its greater surgical risk is justified. Perhaps every surgeon has experienced the necessity of having to lay a kidney more or less widely open in order to find a small stone. We may honestly question the preferability of having allowed that stone to grow to a size more easily localizable, if it has not been so placed as to be obstructive and hence destructive. Repair, even in these cases of extensive surgical injury, is usually satisfactory. But, in another group

in which there has been considerably more, though not total, renal injury, such as with a unilateral large stag-horn calculus, or an obstructive calculus at the ureteropelvic juncture, nephrolithotomy, or even pyelotomy, may be followed by the necessity of nephrectomy later because of subsequent infections, hemorrhage or pain; but examination, even in the absence of such complications, may reveal a practically

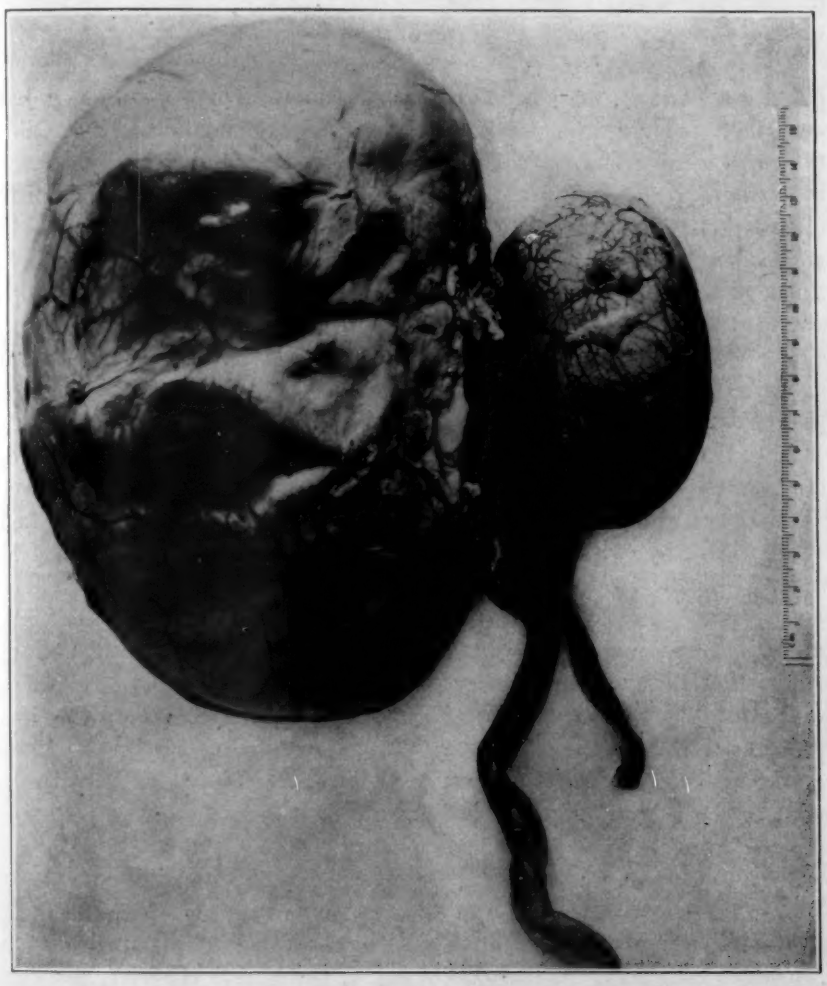

Fig. 25.—Eighteen months simple hydronephrosis in a dog which shows a great increase in size over the hypertrophic opposite kidney; for comparison with hydronephrosis in cat in which there is no increase in size (Fig. 24).

functionless kidney and one in which there has occurred no reformation of stones to account for the loss of activity. The reparatory hypertrophy on the healthy side, which has developed during the period of loss of function on the side injured by the stone before the primary

nephrolithotomy or pyelotomy, prevents the degree of stimulation needed to restore the injured side after removal of the stone and it has suffered a disease atrophy. In cases with likelihood of such a late disuse atrophy, primary nephrectomy, obviously, is preferable.

(*b*) *Ureteral Calculus.*—Clinical examples of renal readjustment are particularly striking in certain cases of ureteral calculus. Not infrequently will a stone completely plug the ureter and some indication of the duration of the complete block be given clinically. Removal of the calculus, in such cases, gives opportunity to study renal counterbalance. During the period of obstruction, the opposite kidney has been doing all the renal work and, if healthy and unaffected by inhibition, will in time undergo a complete compensatory hypertrophy. Some indication of the repair ability of the human kidney after complete obstruction is found in cases of accidental ureteral ligature at operation with subsequent removal of the ligature and study of relative functions. Barney [157] reports a case of accidental ligature of both ureters with good recovery after freeing of the left in two days and the right in six. Caulk [158] performed nephrostomy eight days after complete bilateral ligature with recovery and a spontaneous establishment of ureterovesical drainage sixty-eight days later, but this is a most unusual result and the longest period of complete obstruction with recovery on record. Herman [159] has recently (1923) analyzed a series of twenty-four cases of complete bilateral occlusion, all of a few days' duration, ten treated by nephrostomy, with 50 per cent. primary mortality, eight by surgical removal of the ligature or kink, with 25 per cent. mortality. There was a complete cure in only one case in the first group (Caulk's [158]) and in six in the second. But, of course, these conditions of bilateral obstruction differ from those of unilateral since, in the latter, there is present a good kidney to do the work until the obstructed one has a chance to catch its breath, as it were.

A few brief abstracts will serve to illustrate the types of readjustment that may be expected after ureteral stone.

REPORT OF CASES

Case 1.—A woman, aged 24, had a large stone in the right ureter. She had complained for two years of dull ache in the back and the right side, which came, later, in attacks lasting from eight to ten hours. During the last four weeks, the attacks had been typically ureteral, with radiation down into the groin. Roentgen-ray and urologic study showed stone in the right ureter opposite the ischial spine, with a functionless right kidney. Removal of the stone by

157. Barney, J. D.: The Effects of Ureteral Ligation, Experimental and Clinical, Surg., Gynec. & Obst. **15**:290, 1912.

158. Caulk, J. R.: Ureterovesical Cysts; an Operative Procedure for Their Relief, J. A. M. A. **61**:1685, 1913.

159. Herman, L.: Accidental Bilateral Occlusion of Ureters, J. Urol. **9**: 151, 1923.

cystoscopic means was unsuccessful; it was never possible to pass catheters beyond it. Ureterotomy was followed by almost immediate recovery of right kidney function, from 0 to 12 per cent., in fifteen minutes. In this case, the opposite side had not undergone complete compensation, and the repair ability of the injured side was good, so that counterbalance was a cooperative affair. The ability of response was about equal on the two sides.

CASE 2.—A man, aged 26, had bilateral ureteral calculi, with pain of one year's duration along the course of the right ureter. He had had four severe attacks of renal colic in the last month, each followed by hematuria. Roentgen-ray studies and pyelography showed stones in the lower portions of each ureter. The stones on the left side passed after cystoscopic dilatation. Ureterotomy was required to remove an impacted stone in the right ureter. Observation, three months later, showed remarkable recovery of the previously dilated ureters and kidney pelves with a return of function to normal. This case also illustrates a cooperative type of counterbalance, an even potentiality of response to added stimulation.

CASE 3.—A man, aged 42, had a large ureteral calculus impacted in the lower ureter and infected hydronephrosis above. The stone was removed, but there was failure of repair, continuation of infection and loss of function, which required subsequent nephrectomy. Even after the removal of the obstructing calculus, pyelonephritis persisted and a gradual progressive loss of function occurred, due to the better ability of the opposite kidney to respond by hypertrophic changes to the additional stimulation. A distinctly competitive type of counterbalance followed ureterolithotomy; the potentiality on the two sides was unequal, and a completely compensatory type of counterbalance followed a nephrectomy which removed all opposition or rivalry for work.

CASE 4.—A man, aged 47, had a large stone, completely obstructing the lower, right ureter, and a functionless kidney above, so far as determinable by ureteral catheter. He had suffered the first attack of right-sided pain three years before examination, with periodic lesser attacks since. Urologic study showed small stones in the opposite kidney, but these were nonobstructive, and the function was compensatory. It was a question of nephrectomy or ureterolithotomy and, in view of the doubt as to the length of time the stone in the lower ureter had been completely obstructive, the latter procedure was adopted. Following removal of the ureteral stone, there was no recovery of kidney activity, the kidney apparently having undergone primary atrophy. Cystoscopic study done as long as two years after the removal of the stone, and pyelography showed rather diffuse cystic calcification of the small, atrophic right kidney with absolutely no urinary drainage from it. Recent functional studies, however, showed normal function of the hypertrophic left kidney. This was an example of a complete compensatory type of counterbalance in which primary nephrectomy was indicated.

(*c*) *Hydronephrosis.*—Unilateral hydronephrosis is another condition of renal injury open to repair and presents a surgical problem of importance and frequently, as well, of dispute. It is a common practice to settle the question between a choice of nephrectomy versus a more conservative plastic procedure that will relieve the cause of obstruction and preserve the kidney, by some arbitrary standard of the degree of hydronephrosis, and it is generally believed that sacs above a certain and relatively small size offer too little chance of successful relief to justify conservation, and that large sacs should always

be removed. It also is a general supposition that whatever loss by destruction has occurred is never recovered. Technical failures after conservative surgical attempts, such as persistent fistulas, or infections, requiring subsequent nephrectomy, naturally have tended to lower the standard for such conservation. The surgical decision is too commonly based on a generalized expectation of repair in proportion to the degree of hydronephrosis, whether unilateral or bilateral, and the fundamental principle of renal counterbalance has been entirely overlooked. The degree of hydronephrotic atrophy, of course, is of primary importance since there can be no regeneration of tissue, only an hypertrophy of the uninjured or less injured portions, but, as has been demonstrated experimentally, the relative need of preservation of this reserve tissue in a hydronephrotic kidney is a factor of great importance to the degree and permanence of this reparation. In unilateral cases, the degree of hydronephrotic atrophy of one side ordinarily has a complementary degree of compensatory hypertrophy of the opposite side, and, whenever this is present in a marked degree for both respectively, failure of repair is then not due so much to the fact that repair cannot occur as to the fact that the requisite stimulation for repair is absent. In bilateral cases, on the other hand, an optimum stimulation to repair always exists, and it is therefore in bilateral cases that conservative surgery gives its most brilliant results.

On the basis of such considerations, it would seem preferable to base a decision for or against nephrectomy in unilateral cases not only on the degree of destruction of the side in question, but also on the degree of reparatory counterbalance of the opposite healthy side. Often even with advanced hydronephrosis, the compensatory substitution of function of the opposite side may have been so inhibited that total function is barely covered and no margin of safety exists. Simple nephrectomy has a greater risk in such a case in which opposite compensation is absent than when it is present. This has been long recognized clinically in cases of pyonephrosis with which inhibition of a reparatory hypertrophy of the opposite kidney is common (Albarran [144]), and it is in just such similar and exceptional cases of unilateral hydronephrosis, in which there has been an inhibition of growth of the opposite side, that surgical repair of the hydronephrosis may give the most brilliant results. The proper stimulus for repair is now present. Of two equally advanced grades of unilateral hydronephrosis, one, unaccompanied by a compensatory mate, may show considerable and permanent repair, but the other, accompanied with complete compensation of the opposite kidney, shows no restoration whatsoever after surgery. The question of conservation or radical attack cannot justly be settled by knowing the degree of hydronephrosis and then arbitrarily choosing that size below which conservation is to be practiced and above which, nephrectomy.

Knowing the condition of the opposite kidney gives better judgment. The opposite kidney may have undergone complete compensation or it may have developed a partial compensation only, or it may be doing no more work than it has always done, and in case compensation of it is absent, it makes quite a difference whether this is due to an inhibition of growth or injury by disease or merely to lack of sufficient time for development. Determination of these various conditions is often not possible beforehand with our present methods, but relative functional studies extended over a long period of time, together with a careful and complete diagnosis, suggest many clinical examples of various types of readjustment in unilateral hydronephrosis, and the following abstracts are more or less typical.

TABLE 10.—*Results of Blood Retention and Phenolsulphonephthalein Tests in Case 6*

Date	Urea Nitrogen	Phenolsulphonephthalein Intramuscularly		
		1st Hour	2d Hour	Total
Jan. 4, 1918	168 mg. per 100 c.c.	....	....	....
Jan. 15, 1918	165 mg. per 100 c.c.	....	....	....
Jan. 16, 1918	200 mg. per 100 c.c.	....	....	....
Jan. 17, 1918	214 mg. per 100 c.c.	....	....	....
Jan. 18, 1918	144 mg. per 100 c.c.	....	....	....
Jan. 21, 1918	140 mg. per 100 c.c.	....	....	....
Jan. 23, 1918	112 mg. per 100 c.c.	....	....	....
Jan. 25, 1918	119 mg. per 100 c.c.	1%	4%	5%
Jan. 29, 1918	.....	11%	7%	18%
Feb. 1, 1918	16 mg. per 100 c.c.	11%	7%	18%
Feb. 3, 1918	.....	13%	8%	21%
Feb. 7, 1918	.....	14%	14%	28%
April 10, 1918	....	35%	25%	60%

CASE 5.—A man, aged 24, had a unilateral infected hydronephrosis, with hypertrophic opposite kidney. The relative function, after intravenous injection of phenolsulphonephthalein, for the first fifteen minutes was: right, 30 per cent.; left, no trace of phenolsulphonephthalein. There was no leakage into the bladder. Nephrectomy was performed, as repair of the left kidney was hopeless. These cases are common in practice, and are examples of more or less complete compensatory counterbalance in which conservative procedures are hopeless.

CASE 6.—A man, aged 22, had an infected left hydronephrosis, in which reflex anuria, for several days, followed left pyelography. The total function was 55 per cent. before pyelography. Thorium nitrate was used as the pyelographic medium, and jaundice was pronounced afterward, which was probably due to infectious cholangeitis. The seriousness of the anuria and renal disturbance is shown in Table 10.

The total phenolsulphonephthalein in October, 1919, was only 35 per cent. Following dilatation of the left ureter and preparatory drainage of the hydronephrotic infected sac, the phenolsulphonephthalein rose so that, Jan. 26, 1920, it showed a total of 57 per cent. Following nephrectomy, there was a complete compensatory hypertrophy of the right kidney, total phenolsulphonephthalein, Feb. 6, 1920, being 70 per cent. The patient had remained well. He was married in June, 1924.

This was an example of inhibition of compensatory hypertrophy and a reflex inhibition of function of a potentially healthy kidney by disease abnormality of its mate.

(*d*) *Renal Infections and Tumor.*—Injury from infection on one side is a common cause for inhibition, not only of the normal work of the opposite kidney but also of its growth by hypertrophy. This is recognized as a toxic or chemical type of inhibition, but may be in part also a renorenal reflex. It is frequently observed that, in pyonephrosis and in tuberculosis, a reduced total function is quickly returned to normal after nephrectomy. It is often difficult to differentiate before nephrectomy such a purely inhibitory type of insufficiency from actual insufficiency due to disease, and, although a quick restoration or a failure of restoration afterward may settle the question, it is now too late to correct the early mistake in judgment in the case of failure.

We have had one such misfortune in which the lowered total function was not inhibitory but was due to bilateral disease, and this patient died of renal insufficiency in a few months after nephrectomy. It would have been better at the first operation to have attempted to repair the infected and obstructed kidney than to have removed it. There was advanced pyelonephritis of the opposite side, and not pyelitis with inhibition, which progressed.

Many examples, however, of pure inhibition without renal injury, or permanent injury at least, occur in practice, and the following case is an example with renal tumor and is typical of the condition with various types of other unilateral affections, such as pyelonephritis, perirenal abscess, pyonephrosis and tuberculosis.

Case 7.—A woman, aged 71, with a carcinoma of the right kidney pelvis, had a reflex inhibition of the left kidney. A right nephrectomy was done, and there was compensatory hypertrophy of the left after the operation. The total phenolsulphonephthalein, on admission, was only a trace in two hours, but blood chemistry showed: urea nitrogen, 17 mg. per hundred cubic centimeters; nonprotein nitrogen 30 mg. per hundred cubic centimeters; creatinin 1.27 mg. per hundred cubic centimeters; uric acid, 2.12 mg. per hundred cubic centimeters. A culture of the urine was negative. The ureteral catheter preparation showed no flow from the right kidney, and the function of the left gradually rose so that, in three weeks, the total phenolsulphonephthalein output was 50 per cent. This was an example of reflex inhibition.

3. APPLICATION OF PRINCIPLES OF RENAL COUNTERBALANCE TO SURGICAL PROBLEM OF BILATERAL DISEASE

In most cases of bilateral disease, one kidney is more injured than the other, and the question arises as to which side should have the first surgical attack, as it is rarely indicated to attempt the repair of both at the one operation. Bringing the principles of counterbalance to bear on the problem is often a great help. The pathologic condition producing

the injury on each side relative to the respective insufficiency is the first consideration. In some conditions, it is better to repair the more injured side first; in others, the less injured. Each case should be studied on its own merits, and in most, if not all, cases, repeated preliminary ureteral catheterization studies with their great advantage of preparatory catheter treatment are desirable. Some cases, however, are refractory, and great care must be exercised. They may do better if left alone. Preparatory treatment may be injurious rather than beneficial. And some cases of bilateral stag-horn calculus carry a better prognosis if the patients are not operated on (Geraghty [160]). The improvement in total function, however, is frequently remarkable under catheter preparation, and, in cases complicated by infections, preparatory surgical drainage (nephrostomy) is sometimes indicated when catheter preparation is unsatisfactory or impossible. Such preparatory treatment and studies of relative work form the chief basis of determination of repair possibilities and of decision of the initial attack on the right or left side. Consideration of the relative risk of the operative procedure that will be required for the right or left kidney, and of the relative chances of complete surgical success afterward, is of considerable importance. Occasionally there is no choice.

The following cases exemplify some of the problems met with in bilateral disease:

CASE 8.—A man, aged 38, with bilateral stag-horn calculi in both kidneys, had pyuria for twelve years. He had no renal pain. He had had no previous roentgen-ray examination. He had *Bacillus coli* pyuria. The total phenolsulphonephthalein was 15 per cent. for the first hour, 10 per cent. for the second hour, a total of 25 per cent. Left nephrolithotomy was followed by improvement of total phenolsulphonephthalein to 46 per cent. within a month. Two months later, right nephrolithotomy was followed by improvement of phenolsulphonephthalein to between 50 and 60 per cent. Pyuria persisted, although the condition was improved. The general condition was improved, and has so remained for four years with no recurrence of stones. This was an example of cooperative counterbalance.

CASE 9.—A woman, aged 35, had a chronic *Bacillus coli* pyelonephritis for three years, occurring in attacks with chills, fever and pain. Urologic study showed left hydronephrosis from the kink at the ureteropelvic juncture and milder right hydronephrosis from the movable kidney and kink. There was very definite gradual and progressive diminution in total phenolsulphonephthalein output during the last two or three years, now averaging between 35 and 40 per cent. The relative function varied according to whether the tip of the ureteral catheter had entered the respective pelves or not, as, for example, March 11, 1919, the phenolsulphonephthalein output with the right catheter not up to the right pelvis but the left well in the left pelvis, appeared on the left in five minutes, on the right in eight minutes; the first fifteen minute output on the left was 15 per cent.,

160. Geraghty, J. T.; Short, J. T., and Schanz, R. F.: Multiple Renal Calculi, Unilateral and Bilateral, J. A. M. A. **77**:901-904 (Sept. 17) 1901.

on the right 2 per cent. March 14, with the position of the catheter tips reversed, the phenolsulphonephthalein output on the right, in fifteen minutes, was 10 per cent. and on the left, only 5 per cent. The total phenolsulphonephthalein, March 13, the day before, was 30 per cent. in the first hour after intralumbar injection. April 26, a plastic operation was performed on the left hydronephrosis, and a left nephropexy. Since this operation, there have been recurrent attacks of pyuria with fever, and pain on the right side, diminishing in frequency, however. Repeated studies have shown that the left kidney is always free of infection. Nephropexy of the right kidney has been refused. Pelvic lavage and ureteral dilation have been periodically repeated. Relative function of the right kidney as compared to the left has been gradually diminishing. The total phenolsulphonephthalein output has remained normal, and was 57 per cent., March 14, 1922. March 15, relative function showed an output of 12 per cent. on the right side as against 27 per cent. on the left; there was no pus on the left, but there were from forty to fifty pus cells in every high dry field on the right. During February, 1925, the patient had another typical exacerbation of the right-sided pyelonephritis with fever for three days and renal pain on the right side. A week later relative function showed in fifteen minutes, right, 8 per cent.; left, 29 per cent. This was a good example of competitive counterbalance, the left gradually gaining in functional ability at the expense of loss of ability on the right side, which, in the course of time, may become functionless and the left then completely compensatory.

CASE 10.—A woman, aged 50, with large, bilateral infected hydronephroses, had a total function of 8 per cent. in two hours. The relative function appearance time was: right, eighteen minutes; left, twenty-five minutes. The first fifteen minute output was: right, 6 per cent, left, a trace. Blood urea nitrogen was 19 mg. per hundred cubic centimeters; nonprotein nitrogen was 40 mg. per hundred cubic centimeters. Under ureteral catheter preparation, the phenolsulphonephthalein rose, within one month, to a total of 35 per cent. in two hours, and relative functions of the right had increased to 22 per cent. as compared to a total of 7 per cent. on the left in thirty minutes. October 3, a left ureteral pyeloplasty and nephropexy were done, the large sacular dilated pelvis (Fig. 26) being plicated and a Heineke-Mikulicz incision made at the ureteropelvic juncture. January 23, total function was 51 per cent. in two hours. The left kidney output in fifteen minutes was 30 per cent., as compared to 5 per cent. on the right after ureteral catheterization. The reversed activity of the two sides should be noted. January 25, right ureteropyeloplasty and nephropexy were done, the saccular pelvis being likewise plicated, and the valvular obstruction removed by a Heineke-Mikulicz procedure as for pyloroplasty. It is now two years since the last operation; the total phenoisulphonephthalein remains between 50 and 60 per cent. Pyuria has practically disappeared, and bacilluria is only periodic. The general condition is excellent. The patient has recently undergone successful cholecystectomy for gallstones. There was no renal reaction or disturbance. This was an example of final cooperative counterbalance, with temporary competitive type after the first operation.

SECTION IV. RENAL COUNTERBALANCE IN PROSTATISM

The low function of a prostatic gland may be inhibitory or due to back pressure injury, or the injury of disease either infectious or degenerative, and is probably in most cases a combination affair. The remarkable benefit to kidney function of urinary freedom from reten-

tion by catheter or cystotomy is more responsible than anything else for the low surgical mortality of prostatectomy. This is a type of repair and compensation more or less singular to this group of cases.

Prostatectomists are too prone to regard the kidneys as equally involved in cases of renal insufficiency so frequently complicating con-

Fig. 26 (Case 10).—Left pyelogram, showing a large hydronephrosis with valvelike obstruction at ureteropelvic junction, which was relieved at operation by plication of the thin walled dilated pelvis with silk sutures and a Heineke-Mikulicz incision, to enlarge the ureteropelvic opening as for a pyloroplasty. The right kidney had a similar condition, the pyelogram on this side being almost identical, and was similarly relieved surgically at a second operation. Restoration on the two sides has been even and equal, and total function has returned almost to normal. This is an example of the cooperative type of counterbalance.

ditions of prostatism. This is largely true for the period before relief of obstruction by retention catheter or prostatectomy, but conditions of reparation may differ with the opportunity, and one kidney, through better reserve, less infection or greater freedom from obstruction, may show greater restoration than the other, so that the functional recovery is then mostly unilateral. Relative studies and catheter treatment of each kidney is indicated in practically all cases of insufficiency of total function even when such relative tests show an even injury for both. Persistent pyelonephritis, ureteritis, hydro-ureters or even hydronephrosis (after prostatectomy) should have consideration and treatment, just as much as they would if uncomplicated by prostatism. Treatment must usually be palliative and not surgical, but often a very great benefit follows careful study and catheter treatment of kidney complications both before and after prostatectomy. By no means are all of these cases of renal insufficiency either pure vesical back pressure injuries or progressive nephritides of medical type. Persistent pyuria may be of renal origin and persistent low function may be secondary to this or to a continued ureteral, ureteropelvic or ureterovesical abnormality and therefore be reparable. Counterbalance may be either a cooperation type of bilateral repair, or the competitive type of repair of one, with atrophy of the other. Of a considerable frequency and well worthy of emphasis, however, is a true ascending infection by reason of ureteral antiperistalsis and reflux of bladder contents, which are almost always infected, to the kidney pelvis. These infectious attacks complicate reparatory processes and are often of grave moment. Prostatectomists are all familiar with the sudden rise of temperature and a sore back on one or other side in an old man, at and about the time of closure of his urinary fistula and the reestablishment of urination, particularly if there has been any straining or urethral pain. This is probably an exacerbation or acute onset of a pyelitis or pyelonephritis, as the result of reflux of urine. It has been long known, and Graves [161] has recently experimentally shown how easily and frequently this may occur, and it is probably common in prostatic gland disease both before and after operation.

SECTION V. SUMMARY OF CLINICAL STUDY OF RENAL COUNTERBALANCE

It is seen from the foregoing clinical study that a counterbalance of two kidneys is much more active in the surgical group of renal disease than in the medical. The alterations of disease and of surgery together give greater opportunity for change and adjustment. Nor can the types

161. Graves, R. C., and Davidoff, L. M.: The Choice of Pyelographic Mediums. J. A. M. A. **80**:168-171 (Jan. 20) 1923.

of medical repair be subjected to the same direct methods of testing and observation. It may be possible to so classify and group the conditions as to make a consideration of renal counterbalance of some practical value.

1. FOUR GROUPS OF RENAL TISSUE RELATIVE TO COUNTERBALANCE

For purposes of a consideration of renal counterbalance, renal tissue may be divided into four groups:

1. Normal renal tissue, which has a good reserve power and repair ability, so that with the demand for more work, hypertrophy will occur except when, for some reason, there is an inhibition of growth.

2. Hypertrophic renal tissue, which will undergo, with a greater demand, additional hypertrophy if it has an acquired reserve, or will undergo no change if completely hypertrophic except that lowering of the demand may lead to atrophy.

3. Diseased and injured renal tissue, which with proper stimulation and relief of injury may show repair.

4. Hypoplastic renal tissue, which has no reserve power, and is therefore unable to grow (infantile kidney).

It is evident that the ability of response to the same stimulus of these different groups is frequently both qualitatively and quantitatively unequal. Normal tissue will take on additional work much more readily than hypertrophic or diseased tissue, and if from two to three times its less capable partner in amount, will perform from three to four times or more the amount of work, but if opposed to normal tissue of one-half or one-third its size, as they are now qualitatively equal, each will do an amount proportional to their mass. The principle applies to portions of one kidney as well as to a right and left kidney, although it is this anatomic arrangement that gives counterbalance practical value in surgery. The significance of these changes in the same kidney is emphasized in the section on group hypertrophy. A consideration of the quality of the renal tissue of a right and left kidney is of as much or more importance than of its quantity in the application of renal counterbalance to renal surgery. Even a small normal mass may eventually perform total function if working with an inefficient and slow, though large, mate. The counterbalance of two kidneys, when one or both are altered by disease, is a slow gradual process which may take years for completion, and may never reach an equilibrium. The anatomic changes, whether of repair or atrophy, are progressive, and functional tests indicate relative strength only, so that accurate clinical estimation of an anatomic counterbalance is impossible. The type of counterbalance put into operation by disease or injury, is often completely changed by surgery, and a second surgical

repair may institute a still different type of counterbalance. The alterations in the usual equilibrium of the right and left kidney, brought on by disease or injury primarily and by surgical treatment secondarily, start processes of counterbalance, the end-result of which is dependent on the relative nature or potential reserve strength of the two kidneys and the portions of each.

2. FOUR TYPES OF COUNTERBALANCE

When this consideration is applied to the four groups of renal mass outlined above, four types of counterbalance are definable: (*a*) unilateral counterbalance; (*b*) cooperative counterbalance; (*c*) competitive counterbalance, and (*d*) decompensation.

(*a*) Unilateral counterbalance refers to the growth of one kidney to replace the loss of the other. A complete compensation, in an anatomic sense, is a unilateral compensatory hypertrophy of a functional degree and ability equal to that of two normal kidneys. This never occurs as an acquired condition.

(*b*) Cooperative counterbalance refers to a more or less equal apportionment of work after any particular alteration. The ability of response of the two kidneys is qualitatively similar, although they may differ in size. There need not be bilateral injury for cooperative counterbalance, provided the unilateral injury has not been diffuse, and it seldom is, or has not been so great as to be irreparable.

(*c*) Competitive counterbalance is a type present between kidneys of distinctly different reserve or potential strengths. The ability of response to the same stimulus is much greater in one than the other. There will result a gradual accumulation of work to one with gradual proportional loss to the other. One grows, the other atrophies. The final counterbalance is necessarily compensatory. Case 9 is an example of competitive counterbalance now active, but which may become unilateral when the right undergoes destruction by reason of the infection present and the competitive loss of functional stimulation; or cooperative, when this competition is removed with relief of the right-sided infection and hydronephrosis by nephropexy.

(*d*) Decompensation refers to failure of a counterbalance and is indicated functionally by renal insufficiency. The total renal mass, whether of one or two kidneys, has either undergone a maximal degree of hypertrophy which is insufficient to care for total function, or the renal tissues may have been so injured as to be unable to respond to the additional stimulus. Often, in the latter case, removal of the cause of injury will permit of sufficient repair to give complete counterbalance.

In none of the few cases abstracted above were both kidneys normal to start with. The primary disturbance was unilateral in some and bilateral in others. With few exceptions, operation always brought

about a complete change in the type of counterbalance, in most cases favorable to conservation; as, for example, the change from a competitive process, in which reparation on one means loss on the other side, to a more beneficial cooperative state, with reparatory growth of both.

3. PRACTICAL APPLICATION OF A CONSIDERATION OF COUNTERBALANCE TO RENAL SURGERY

The clinical practicability of renal counterbalance to renal surgery is obvious. In unilateral disease, surgical repair of an injury of such duration and extent as to have caused opposite compensatory hypertrophy is almost always doomed to failure. The only exceptions will be in cases of early disease in which surgery was so technically perfect as to have removed all cause of injury, as in ureteral stone, or early and uninfected hydronephrosis. Even in such cases, often good technical treatment is not quite good enough to secure permanent repair. Nevertheless, renal reparation is sufficiently strong to justify conservative surgery in many unilateral conditions, and careful consideration of the principles of counterbalance will permit of greater success in their selection.

In bilateral disease, conservative renal surgery is always indicated. Consideration of the potential ability of the right and left side to repair, together with the relative risk of the respective operative procedures, and the relative chance of successful operative relief, will materially improve judgment in selection of the side for the initial attack. The successful repair of one side institutes a competitive type of renal alteration of importance for careful consideration relative to operations on the other kidney. If the opposite injury is silent, delay in subjecting the patient to the risk of a second operation may be advisable, but, in order to make it so, the success of the initial repair operation must have been such as to make this kidney perfectly capable of performing total function, as continuation of the injury on the other will soon lead to complete loss and atrophy of the latter so that now, should operation become necessary, the only logical procedure would be nephrectomy. In bilateral disease, in order to get a cooperative type of bilateral repair, therefore, the two repair operations should have an intervening period just sufficiently long to allow of complete convalescence from the first. A prolonged period materially reduces the chance of a successful result of the second operation. A partial or incompletely successful initial repair operation renders the possibilities of repair in the opposite kidney greater. And the technical success of the second operation may be so much greater than the first that the second kidney eventually becomes the compensatory side, and the first will have either to be subjected to a secondary repair operation or suffer elimination by atrophy or removal.

GASTRIC MOTILITY

III. THE MECHANISM OF THE PYLORUS *

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I. RELATION OF ANTRAL CONTRACTION TO THE PYLORIC MECHANISM

Cannon's [1] theory of the acid control of the pylorus has long been accepted by numerous physiologists. Briefly stated—it will be referred to again later—he holds that the pylorus is closed during digestion, that an acidity of 0.2 per cent. on the gastric side brings about its opening, and that the presence of acid in the duodenum effects its closure. The antral waves sweep on repeatedly to the pylorus, but this gateway remains closed until the continued secretion of hydrochloric acid brings up the concentration of the acidity to the level indicated above. The pylorus then opens and the next advancing wave forces the antral contents into the duodenum.

But after studying numerous dogs [2] by the method previously described, it seemed that this theory could not explain some of the observations that were made. For it became more and more obvious that every wave that progressed to the pylorus forced gastric chyme into the duodenum. Take for instance the following experiment.

PROCTOCOL

EXPERIMENT 1.—Dog 1 was fed 375 c.c. of soup containing meat and bones at 1:30 p. m., April 20, 1922. The abdomen was opened by a transverse incision under light ether anesthesia at 2:10 p. m. Retrograde peristalsis in the antrum was immediately noticed. This persisted for five minutes. Palpation revealed a bone in the antrum. This was pushed by hand into the body. After a few minutes waves began coming down from the body, starting opposite the cardia. The rate was four per minute. When the waves reached the angle there was a deep constriction almost cutting the stomach into two parts. There followed a systolic contraction of the entire antrum, involving both circular and longitudinal muscles; but the contraction of the proximal part of the antrum seemed to be a little ahead of the distal. As the antrum con-

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* From the laboratories of the Department of Surgery of the Columbia University College of Physicians and Surgeons. The methods used in these studies have been fully discussed in the first paper of this series.

1. Cannon, W. B.: The Mechanical Factors of Digestion, New York, 1911, p. 101.

2. Klein, Eugene: Gastric Motility, I, The Origin and Character of Gastric Peristalsis, Arch. Surg. **12**:571 (Feb.) 1926.

tracted, fluid and air could be heard and felt being squeezed into the duodenum. Every contraction of the antrum was accompanied by a gurgle. Occasionally a contraction started at the angle and was followed by a contraction of the whole antrum. At other times a wave coming down from the body stopped at the angle and was not followed by any contraction beyond. But the typical sequence was as above.

Again and again it was evident from watching all the dogs that every wave that progressed to the pylorus forced contents of the antrum into the duodenum.[3]

In 1913, Cole[4] reported at the meeting of the American Medical Association that from a large number of serial roentgen-ray studies in man he was forced to the conclusion that each advancing peristaltic wave propels chyme into the duodenal cap, and that "there is no roentgenological evidence in man of a periodical opening and closing of the pyloric valve independently of each gastric cycle, as described by Cannon." Cannon's work was done with cats. Cole's work was confirmed by McClure, Reynolds and Schwartz,[5] who also observed the stomachs of normal men through the fluoroscope. They felt, as he did, that the pylorus opened as each and every wave reached the sphincter to permit the passage of chyme into the intestine. And this was true no matter whether fats, carbohydrates or proteins were used in their tests. Reynolds, Lawrence and McClure[6] later again confirmed this work.

In addition to these facts elicited by the roentgen ray, there is very good experimental evidence pointing in the same direction. Kirchner and Mangold[7] introduced a balloon into the antrum of the stomach through either a gastric or a duodenal fistula and then recorded the contractions on a smoked drum. They then fed the animals and again recorded the rhythm of the gushes from the duodenal fistula. As both these rhythms were the same, they concluded that every antral contraction was followed by the propulsion of fluid through the pylorus.

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3. Contraction of the antrum as a whole is described here, but the same phenomenon was found with the progressive peristaltic wave (character of gastric peristalsis[2]).

4. Cole, L. G.: The Physiology of the Pylorus, Pilleus Ventriculi, and Duodenum as Observed Roentgenographically, J. A. M. A. **61**:762 (Sept. 6) 1913. Motor Phenomena of the Stomach, Pylorus and Cap Observed Roentgenographically, Am. J. Physiol. **42**:618, 1916-1917.

5. McClure C. W.; Reynolds, L., and Schwartz, C. O.: On the Behavior of the Pyloric Sphincter in Normal Man, Arch. Int. Med. **26**:410 (Oct.) 1920.

6. Reynolds, L., and McClure, C. W.: Motor Phenomena Occurring in Normal Stomach, in the Presence of Peptic Ulcer and Its Pain, as Observed Fluoroscopically, Arch. Int. Med. **29**:1 (Jan.) 1922.

7. Kirschner and Mangold: Die motorische Funktion des Sphincter Pylori und des Antrum Pylori beim Hunde nach querer Durchtrennung des Magens, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **23**:446, 1911.

Luckhardt, Phillips and Carlson,[8] using a somewhat similar technic, recorded simultaneously the issuing of drops from the duodenal fistula and the contractions of a balloon in the stomach. The fluid was introduced into the stomach through a gastric fistula. Their tracings show that every peristaltic wave was accompanied by a discharge of fluid through the duodenal fistula.

And recently Wheelon and Thomas [9] have advanced still more direct evidence. Through an incision in the fundus of the stomach, they inserted an apparatus containing a separate balloon for the pylorus and for the antrum, and then recorded the contractions of these parts on a smoked drum. They found that the antral contraction always occurred during a stage of pyloric relaxation. Further, when the pylorus had reached its height of contraction, the antrum in turn had returned to a state of relaxation. They conclude that the activities of the pyloric sphincter are in great part dependent on the activities of the antrum, and that during the digestive processes the impulse to contract in the antrum is propagated into the sphincter. They also state that if acid acts to regulate the pylorus, it must also act in a similar way on the antrum and stomach, for the motility of the antrum determines the motility of the pylorus.

It therefore seems justifiable to conclude from roentgen-ray evidence in animals and in man, and from experimental evidence in animals that the pylorus is normally open at the height of antral contraction, and that every antral contraction is normally followed by the discharge of chyme through the pylorus. Of course, this is at marked variance with the conclusions of Cannon from his studies with cats.

II. MECHANISM OF THE PYLORUS

Krehl,[10] in his admirable book on pathologic physiology, states that the function of the stomach is to prepare food properly for the intestine where the chief phenomena of digestion take place. Three of the more important processes in that preparation are: to fluidify the food, to bring it to the proper reaction, and to approximate its temperature to that of the body. In other words, the stomach effects on its contents if necessary a mechanical, a chemical and a thermal change.

The pylorus is the gateway at the threshold of the intestine. Concerning its mechanism of action there are several theories. All are

8. Luckhardt, A. B.; Phillips, H. T., and Carlson, A. J.: Contributions to the Physiology of the Stomach; the Control of the Pylorus, Am. J. Physiol. **50**:57 (Oct.) 1919.

9. Wheelon, H., and Thomas, J. E.: Observations on the Motility of the Antrum and the Relation of the Pyloric Sphincter to that of the Antrum, J. Lab. & Clin. Med. **6**:124 (Dec.) 1920.

10. Krehl, L.: Pathologische Physiologie, Ed. 11, Leipzig, 1921.

agreed, however, that following the entrance of food into the stomach and during the progress of digestion, it is closed, and that it opens from time to time to permit the onward passage of the gastric chyme into the duodenum. If that is so, it is necessary to assume that some stimuli act at intervals to open it. With normal food, these stimuli must be either (*a*) chemical, (*b*) mechanical or (*c*) thermal. We shall discuss these stimuli in this order.

A. QUESTION OF CHEMICAL CONTROL OF THE PYLORUS

Effect of Physiologic Dilutions of Acids in the Stomach on the Pylorus.—Among the chief theories of control of the pylorus is one advanced by Cannon.[1] As quoted from his book it is as follows:

> The pylorus is tonically closed when food is ingested, and remains closed against recurring pressure. The appearance of acid at the pylorus causes the sphincter to relax. The pressing peristaltic waves now force some of the acid chyme into the duodenum. The acid in the duodenum at once tightens the sphincter against further exit. The same acid also stimulates the flow of alkaline pancreatic juice. Since no inorganic acid is normally present beyond the first centimeters of the small intestine, and since the acid reaction of the contents in this uppermost region is replaced throughout the rest of the small intestine by practically a neutral reaction, the acid chyme must be neutralized soon after its emergence from the stomach. As neutralization proceeds, the stimulus closing the pylorus is weakened; now the acid in the stomach is able again to relax the sphincter. Again the acid goes forth, and immediately closes the passage behind until the duodenal processes have undergone their slower change. And thus repeatedly until the stomach is empty.

The essence of Cannon's theory is, first, that the discharge of foodstuffs is "occasional," and, second, that this irregularity is determined by the time necessary for the acid to reach the proper reaction on the gastric side to open the pylorus, and then by the time necessary to neutralize the acid when it has reached the duodenum.

But there is now a large amount of evidence pointing strongly to the conclusion that the usual chemical reactions in the stomach do not control the pylorus in the manner that Cannon believed. This evidence may be divided into three groups, (*a*) roentgenologic, (*b*) clinical and (*c*) experimental.

(*a*) In the previous section it was shown that Cole has demonstrated with the aid of the roentgen ray that following the approach of each antral wave to the pylorus chyme was forced through that sphincter. McClure, Reynolds and Schwartz [5] found the same thing with their fluoroscopic studies, and the experiments of Luckhardt, Phillips and Carlson [6] also confirm these findings. This evidence obtained by means of the roentgen ray was shown in the previous section to be confirmed by other methods of experimentation. It is, of course, directly opposed to Cannon's findings of irregularity in the intervals of discharge.

(*b*) The clinical evidence against the theory is found in the condition of achylia gastrica. Here although there is an absence of acid, the food, whether it be neutral, alkaline or acid, passes on into the duodenum. Cannon [11] answered this by saying that it was possible for the organism to adapt itself to abnormal conditions. But that explanation is perhaps not applicable here, for, as will be later shown, food not only leaves the abnormal stomach under these conditions but may also leave the normal stomach in a neutral or alkaline state. And it may do that without any previous preparation whatever, as, for instance, the first time an alkaline meal is administered. This will be discussed in detail later.

(*c*) The experimental evidence against the theory is as follows: It has long been known that water and egg white may leave the stomach in a neutral condition. That was determined by studies on dogs with duodenal fistulas. Among many others who worked on this problem may be mentioned Hirsch,[12] von Mering,[13] Moritz,[14] London and Sulima,[15] and Ivy.[16] They are agreed that water given by mouth emerged almost at once from the duodenal fistula. Obviously if an acidity of 0.2 per cent. hydrochloric acid was necessary to open a closed pylorus, this rapid emptying could not occur.

Cannon [17] concedes these facts concerning water and egg white. He cannot, however, make them coincide with his theory and assumes that the presence of these substances is accompanied by a low pyloric tonus that permits of their rapid discharge. Fats, too, do not excite gastric secretion, yet they leave the stomach.

If the pylorus opens only when the acidity reaches a certain level, we would expect that if we were to dilute the gastric contents with a neutral fluid and thus markedly depress the acidity, the emptying would be delayed until the continued secretion of hydrochloric acid had once more brought the reaction up to the proper level. But that does not occur. If fluid is given to an animal at the height of a meal, the fluid very rapidly

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11. Cannon (Footnote 1, p. 128).

12. Hirsch: Untersuchungen über den Einfluss von Alkali und Säure auf die motorischen Funktion des Hundemagens, Centralbl. f. klin. Med. **14**:73, 1893.

13. Von Mering: Ueber die Funktion des Magens, Verhandl. d. Cong. f. inn. Med. **12**:471, 1893; ibid. **15**:433, 1897.

14. Moritz: Studien über die motorische Thätigkeit des Magens, Ztschr. f. Biol. **24**:565, 1901.

15. London and Sulima: Zur Chemismus der Verdauung im tierischen Körper: Eiweissverdauung im Magendarmkanal, Ztschr. f. physiol. Chem. **46**: 233, 1905.

16. Ivy, A. C.: Studies in Water Drinking, Am. J. Physiol. **46**:420 (July) 1918.

17. Cannon (Foonote 1, pp. 117-118).

runs out of the stomach. Thus Moritz [14] after feeding sausage to a dog with a duodenal fistula, found that only 18 c.c. of fluid was recovered from the fistula over a period of one and one-half hours. If 20 c.c. of water was then given, there was very soon a gush of clear fluid from the fistula; this was repeated at intervals. To say that the water passes out through a channel along the lesser curvature does not minimize the force of this argument, for it must pass through the antrum, and can there effect a dilution of the acidity.

That alkaline fluid may leave the normal stomach of man is shown in the work of Spencer, Meyer, Rehfuss and Hawk.[18] When the Rehfuss tube had been passed, they gave their patient 100 c.c. of a 5 per cent. sodium bicarbonate solution. Aspiration of a small quantity for titration every twenty minutes showed that the stomach had emptied itself although the reaction had never become acid.

Then there is the work of McClure, Reynolds and Schwartz.[5] They kept the reaction in the first portion of the duodenum acid by the injection of hydrochloric acid through a duodenal tube. Nevertheless, under the roentgen ray they could see that each wave in the stomach forced barium over into the duodenum, in spite of the acid there, and when according to Cannon's theory the pylorus should have been tightly closed.

There is then no doubt that food may leave the stomach although no free acid is present in that organ, and this fact is true in both the healthy and the pathologic stomach. As will be remembered, we have assumed that following the entrance of food into the stomach the pylorus closes or, in the words of Cannon, "the pylorus is tonically closed when food is indigested." If the pylorus is closed, and yet, in the absence of free acid, food leaves the stomach, then some other factor must have caused it to open. What that factor may be will be discussed later.

Effects of Abnormal Dilutions of Acids on the Pylorus and on Gastric Peristalsis.—Having discussed the effects of normal concentrations of free acid on the pylorus, I shall now consider the results produced by the higher dilutions and incidentally their effect on gastric motility. It has long been known that acids delay gastric emptying. Hirsch, in 1893, found in his experiments with dogs possessing a duodenal fistula that if distilled water was given by mouth the stomach began to empty itself almost immediately through the fistula and that from 300 to 400 c.c. was discharged in from ten to twenty minutes. Weak alkaline solutions left just as rapidly. On the other hand, if the same quantity of from 0.1 to 0.2 per cent. hydrochloric acid was used, some of the solu-

18. Spencer, W. H.; Meyer, G. P.; Rehfuss, M. E., and Hawk, P. B.: Direct Evidence of Duodenal Regurgitation and Its Influence Upon the Chemistry and Function of the Normal Human Stomach, Am. J. Physiol. **39**:459 (Feb.) 1916.

tion was still present in the stomach at the end of one hour. If the concentration was increased to from 0.3 to 0.5 per cent., then from one-half to two-thirds was still retained after the same interval. If 1 per cent. hydrochloric acid was used, for from five to ten minutes very small quantities entered the duodenum; then expulsion stopped and profuse vomiting followed. Ortner's [19] results with the same method were very similar, and Morse,[20] using a somewhat different technic, also found that the rate of the emptying time diminished as the acid concentrations were increased. These results are in accordance with those of other writers, and it seems fairly well established that the higher concentrations of hydrochloric acid delay gastric emptying.

What causes this delay? In his book Cannon [21] called attention to the fact that two possible factors may be responsible for the discharge of gastric contents: one is the recurring peristaltic wave, and the other the patency of the pylorus. He justly criticized the older workers for not distinguishing between these. In their experiments with duodenal fistulas, if chyme ceased spurting from the fistula following experimental interference, they concluded that the cessation of flow was due to closure of the pylorus. Yet absence of peristalsis could have produced the same result even with an open pylorus. But when working with the duodenal fistulas alone, one cannot say which of these two causes is responsible for the retention of the gastric contents. Cannon, of course, believed that the acid in the duodenum effected a closure of the pylorus until it was neutralized by the intestinal contents. Whether this is so will be fully discussed later. But does the acid produce any effect on the second factor? Does it cause any delay in peristalsis? Not many observations are available to answer this question. Yet those we have seem quite significant.

Among them are those of Schicker,[22] who, after ascertaining in fifty-two normal subjects that the average length of time for a wave to travel across the stomach is 20.4 seconds, found that in hyperacidity the interval is 22.5 seconds and in hypo-acidity or achylia 18.5 seconds. In other words, with hyperacidity there is a slowing of the gastric rate. A similar finding was observed by McClure, Reynolds and Schwartz [5] in their work with a duodenal tube. With the end of the tube at the antral side of the pyloric sphincter, they introduced 20 c.c. of 1 per cent. sodium bicarbonate solution through it. An acceleration of gastric

19. Ortner: Beitrag zur Kenntnis der Magenentleerung, Arch. f. d. ges. Physiol. **168**:124, 1917.

20. Morse, W. E.: The Relation of Acid to Gastric Discharge and Duodenal Regurgitation in the Dog, Am. J. Physiol. **41**:439 (Oct.) 1916.

21. Cannon (Footnote 1, p. 99).

22. Schicker: Roentgenuntersuchungen über Form und Rhythmus der Magenperistaltik beim Menschen, Deutsch. Arch. f. klin. Med. **104**:566, 1911.

peristalsis followed immediately, that is, the duration of the wave was decreased from twenty-two seconds to thirteen. Neutralization of the acid present therefore resulted in a marked increase of the rate.

Then Carlson,[23] as a result of his observations on a man with a gastric fistula, reported that "the rhythms of the empty stomach make their appearance whether the stomach mucosa is acid or alkaline in reaction, but that strong acidity or alkalinity caused inhibition." A 0.5 per cent. solution of hydrochloric acid caused greater inhibition than a similar concentration of sodium bicarbonate. There is a slow secretion of gastric juice during the contractions, but a rapid secretion of gastric juice is accompanied by a depression of the contractions. Further observations [24] on the same man showed that all acids caused inhibition of the movements and decrease in tonus of the empty stomach when introduced directly into the gastric cavity. The duration of this inhibition was proportionate to the concentration and to the total quantity of acid introduced. Two hundred cubic centimeters of 0.5 per cent. hydrochloric acid solution could cause complete inhibition of the contractions and relaxation of the tonus for from forty to sixty minutes, whereas the same quantity of 0.25 per cent. hydrochloric acid solution usually inhibited for a period of only twenty-five or thirty minutes. Weak concentrations of acid did not inhibit the contractions. He repeated these experiments with normal gastric juice obtained from the patient himself. "The degree of inhibition produced . . . was the same as that caused by an equal quantity of hydrochloric acid of a concentration equal to the free acidity of the gastric juice. It would thus seem that the hydrochloric acid in the gastric juice constitutes the stimulus that leads to the inhibition." Of course, one must remember that the high concentrations mentioned above are not those which normally are present during the course of digestion. And so one of his further findings does not seem contradictory, namely, that the movements of the stomach in digestion are not inhibited by the acids in concentrations equal to that of the gastric juice. During digestion the acid is diluted by the food and other factors which shall be considered later.

But long before any of the foregoing experiments had been done, Ducceschi [25] in 1897 obtained similar results. He worked with dogs in which he had produced a gastric fistula. He inserted a balloon through this fistula into the antrum of the stomach. He then injected a 0.1 per cent. solution of hydrochloric acid in the vicinity of the balloon. Marked slowing of the rhythm of the contractions followed. Stronger solutions

23. Carlson, A. J.: The Character of the Movements of the Empty Stomach in Man, Am. J. Physiol. **31**:151, 1912-1913.

24. Carlson, A. J.: Influence of Stimulation of the Gastric Mucosa on the Contractions of the Empty Stomach in Man, Am. J. Physiol. **32**:245, 1913.

25. Ducceschi, quoted from Luciani: Physiologie des Menschen, Jena, **2**: 167, 1906.

caused irregularities in the rhythm and a weakening of its intensity. If the strength of the acid was still further increased, the contractions ceased or retrograde peristalsis set in. In the cardia, on the other hand, solutions of from 0.1 to 0.5 per cent. seemed to have an augmentor effect.

And Kaplan [26] in St. Petersburg, using an entirely different experimental method, came to the same conclusion, namely, that hydrochloric acid stimulates the fundus and inhibits the antrum. It will be remembered, of course, that the chief work of the antrum is motor.

Bearing further on this problem is Experiment 1 outlined above. Fifty cubic centimeters of 1 per cent. hydrochloric acid solution was passed into the stomach of a dog who one hour previously had been fed a full meal. Before the hydrochloric acid was given, the waves were seen by direct observation to pass down the stomach at the rate of four per minute. As the total volume of the meal that had been fed was 750 c.c. there naturally occurred a dilution of the hydrochloric acid. A similar experiment was performed on dogs with an empty stomach.

EXPERIMENT 2.—In Dog 2, the right and left vagi were sectioned, May 11, 1922.[2] May 17, the dog received no food. The abdomen was opened, May 18, at 3:20 p. m. One hundred and fifty cubic centimeters of 1 per cent. sodium bicarbonate was immediately passed into the stomach through a tube. Very weak peristaltic waves were noted running all the way down to the pylorus. The stomach was washed at 3:30 p. m. At 3:34 p. m. 150 c.c. of 1 per cent. hydrochloric acid solution was passed into the stomach through a tube. Contractions were seen at once, starting with a constriction at the level of the angle and followed by a systolic contraction of the antrum as a whole. This was repeated twice. Then retrograde waves starting at the pylorus followed. The pylorus contracted first and then a contraction wave ran up to the angle, but the distal portion of the antrum remained very firmly contracted so that the entire antrum was like a hard white cord. Accompanying this retrograde wave was a gush of vomitus. This retrograde wave was repeated three times more, and each time there was a gush of vomitus. The stomach then remained perfectly quiet. The duodenum was not seen as it was overlain by the antrum. A tube was passed into the stomach at 3:43 p. m. and 40 c.c. of dark bile stained fluid was obtained. At 3:44, 1 per cent. sodium hydroxid was passed into the stomach through a tube. Weak peristaltic waves running down to the pylorus were noted. An occasional retrograde wave running from the pylorus to the angle also was seen. No vomiting occurred. At 3:55 the antrum was gently pulled a little to the right. In the duodenum, about 4 cm. from the pylorus, a retrograde wave was seen to start and to run up to the pylorus. At 3:50, 10 c.c. of brownish fluid was obtained through a stomach tube.

Several exceedingly interesting observations not bearing exactly on the facts we are at present discussing may be briefly mentioned. First is the mechanism of the vomiting that occurred when there was a large

26. Kaplan: Zur Lehre über den Einfluss der chirurgischer Veranderungen des Magens auf die Verdauungsprozesse, Ztschr. f. physiol. Chem. **87**:313, 1913.

abdominal incision and the abdominal muscles could not contract. Then the presence of bile in the gastric contents after the withdrawal of the hydrochloric acid showed that there had been a regurgitation of intestinal fluids. This will be referred to again. Finally, the observation of a retrograde peristaltic wave in the small intestine showed that this type of wave may occur there and that intestinal regurgitation is probably to some extent at least the result of such a phenomenon.

But now we are interested in the effects of acid on gastric peristalsis. To summarize the results obtained above: In the first experiment, when 1 per cent. of hydrochloric acid solution was placed in a stomach containing a large amount of food, and hence was diluted, the rate of peristalsis slowed to one-half what it previously had been. In the second experiment, when 1 per cent. hydrochloric acid solution was placed in an empty stomach, three waves carrying the gastric contents toward the duodenum were followed by retrograde waves which caused vomiting, and which were followed by complete cessation of gastric peristalsis.

We have thus far found that acids beyond a certain concentration delay gastric emptying; that at the same time there is a slowing of the gastric peristalsis; that the effect is directly proportional to the concentration and that if the strength of the acid is still further increased there is a cessation of peristalsis and vomiting after some of the material has passed into the duodenum.

The next question of interest is, what site does the hydrochloric acid stimulate to produce this slowing of peristalsis? A great amount of experimental work has been done to ascertain the relationship of chemical stimulation in the duodenum to the pyloric reflex, but little is known as to the effect of such stimulation on gastric peristalsis.

Bearing on the latter problem are some observations of Kirschner and Mangold.[7] Through a gastric fistula they inserted a balloon connected with a recording apparatus into the antrum of the stomach and traced the antral contractions graphically on a smoked drum. They found that if they injected 20 c.c. of 0.36 per cent. hydrochloric acid solution into the duodenum there was a cessation of antral contractions for two and one-half minutes. If a larger quantity was used, then there was a prolonged inhibition. Eight-tenths per cent. sodium chlorid solution did not have this effect. On the other hand, olive oil also was found to cause inhibition.

Then there is a finding made by Reynolds, Lawrence and McClure,[8] who by means of the fluoroscope, observed the stomachs of men after a barium meal and with a duodenal tube in situ. In a patient with a duodenal ulcer, cessation of gastric peristalsis followed the pouring of some tenth normal hydrochloric acid into the duodenum through the tube, and at the same time duodenal antiperistaltic waves were set up.

The fact that a duodenal ulcer was present in this patient should not detract from the value of this observation since it is in entire accord with the experimental evidence outlined above. And also there is further confirmatory data in an earlier paper of McClure, Reynolds and Schwartz.[5] Here, too, a duodenal tube was in place in the first portion of the duodenum. In two subjects the introduction of twentieth normal hydrochloric acid was followed by duodenal antiperistalsis with either prolonged pylorospasm or almost complete cessation of antral peristalsis. In two other cases following a similar experiment, after a short latent period, there was a marked weakening of the waves. No mention is made as to whether any change in rate was observed.

It would seem that the effects noted above of an irritant concentration of hydrochloric acid, namely, slowing of the gastric peristaltic waves, and perhaps a diminution in their tone, are due to a reflex from the duodenum. It is well known that the duodenal mucosa is far more sensitive than the gastric, and not alone to chemical but also to mechanical stimuli. Although the latter stimuli will be more fully considered later, I may quote from Luckhardt, Phillips and Carlson:[8] "Vomiting is elicited with the greatest ease by any irritation of the duodenum," and "reflex emesis is certainly more readily elicited from mechanical irritation of the duodenal mucous membrane near the pylorus than from simple irritation of the gastric mucosa. Salivation and retching precede the act." McClure, Reynolds and Schwartz[5] found that any slight movement of the metal tip in the duodenum caused by pulling on the tube would cause cessation of peristalsis in the stomach. These and other facts to be discussed later add additional weight to the conclusion arrived at above. It will also be remembered that in the experiment on Dog 2 outlined above, in which a solution of 1 per cent. hydrochloric acid was poured into the stomach, there were three movements of expression into the duodenum before vomiting occurred. When Hirsch,[12] in his work with dogs on which he had previously performed a duodenal fistula, passed 1 per cent. hydrochloric acid solution into the stomach through a tube, for from five to ten minutes small quantities entered the duodenum and were expelled through the fistula, then expulsion stopped and profuse vomiting followed. In other words, it would seem that vomiting occurred only after the irritant solutions had reached the duodenum. I would not be prepared to say that still stronger irritation of the gastric mucosa could not set up efforts of expression before any material had entered the duodenum.

We have thus far found that solutions with physiologically non-irritating reactions, whether they are acid, neutral or alkaline, may pass through the pylorus; that if the pylorus is closed, an acid reaction is not necessary to open it; that higher concentrations of acids cause definite delay, and that this delay is in part, at any rate, due to slowing of the

gastric peristaltic rate; that even in the concentrations normally encountered there may be a difference of four seconds in the rate of waves in hyperacidity and hypo-acidity, the former being the slower; that the site stimulated by the acid is probably the duodenum; that if very strong acids are used peristalsis is completely inhibited and there may be reverse peristalsis and vomiting. It is possible that at the same time there is some action on the pylorus, that is, that strong acids in the duodenum increase its tone, but, as stated before, no experiments with fistulas alone can be advanced as proof of that contention. The whole mechanism is apparently to protect the duodenum from undue irritation. From that point of view it is hard to see why weak alkalis or neutral solutions should be kept back in the stomach, and one can readily see why the strong acids should be either retained till neutralized or expelled by vomiting.

Effect of Physiologic Concentrations of Acids in the Duodenum on the Pylorus.—Cannon's theory, it will be remembered, is made up of two parts: first, that acids on the gastric side open the pylorus, and, second, that acids on the duodenal side hold it closed. We have seen that acid on the gastric side is not necessary to open the sphincter. We shall now consider whether acid on the duodenal side holds it closed.

The control of the pylorus by acid in the duodenum is in itself widely accepted as a sufficient theory of pyloric control. It is often called the Hirsch-von Mering theory. The mechanical features of this theory will be considered later. In its chemical phase, the acid is believed to close the pylorus when it reaches the duodenum and to hold it until the acid has been neutralized. The sphincter then relaxes and a fresh supply of chyme is again forced into the duodenum; the acid in the chyme again closes the pylorus, and so on. In this country, Spencer, Meyer, Rehfuss and Hawk [18] asserted adherence to the foregoing theory.

It seems very probable that acid on the duodenal side is just as unnecessary for the mechanism of emptying the stomach as it is on the gastric side. And the evidence for this belief is as follows: First, the mechanism of the pylorus functions without acid under the following conditions:

(*a*) In achylia. Here, of course, there is no acid yet the pylorus opens and closes to permit the passage of chyme. The latter theory can in no way explain this fact. It must be confessed that here is an exception to the rule.

(*b*) During the early course of digestion. The Rehfuss test meal often shows that free hydrochloric acid does not appear in the gastric contents until fifteen minutes or longer after the ingestion of food. Roentgen-ray observations show that food ingested begins to leave the stomach at once or within a few minutes.[5] Evidently, therefore, food

material does pass through the functioning pylorus when no acid is present. And we can mention again that even Cannon agreed that the pylorus opens and closes to permit the egress of milk, egg white and fats in the absence of acid.

(*c*) Spencer, Meyer, Rehfuss and Hawk [18] gave a patient an alkaline solution and then withdrew samples from the stomach at regular intervals to test the reaction; they found that the stomach had emptied itself although the reaction had never become acid.

Second, the experimental introduction of acids directly into the duodenum does not necessarily close the sphincter and keep it so. Of course, hydrochloric acid is an irritant to the duodenum, and, as detailed below, conclusions must be very carefully drawn from its experimental use. Nevertheless, in concentrations higher than it is normally known to exist in the duodenum it does not keep the pylorus closed. Thus,

(*a*) McClure, Reynolds and Schwartz [5] found that the injection of acid into the duodenum through a duodenal tube did not prevent the orderly opening and closing of the pylorus and the discharge of barium through it.

(*b*) The following experiment was performed by me. The method of preparation of the dog was that described in a previous paper.[2]

EXPERIMENT 3.—Dog 3 was fed 500 c.c. of soup containing meat at 1:35 p. m., March 2, 1922. A transverse upper abdominal incision was made under light ether anesthesia at 2:15 p. m. Peristalsis was present in the stomach. At 3 p. m. 2 c.c. of 2 per cent. soda bicarbonate solution was injected into the antrum just proximal to the pylorus with a hypodermic syringe and a very fine needle. No effect was seen on the opening and closing of pylorus. At 3:10 p. m. 1 c.c. of 0.3 per cent. hydrochloric acid solution was injected into the duodenum 0.5 cm. beyond the pylorus. No effect on the opening and closing of the pylorus was seen.

In view of all this evidence, it seems justifiable to conclude that the pyloric mechanism may function without the presence of hydrochloric acid in the duodenum. Those who have believed that it is necessary have drawn their chief support from the work of Hirsch,[27] von Mering,[13] Serdjukow [28] and Tobler.[29] In view of the wide quotation of

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27. Hirsch (Footnote 10); Beiträge zur motorischen Funktion des Magens beim Hunde, Centralbl. f. klin. Med. **13**:993, 1892; Weitere Beiträge zur motorischen Funktion des Magens nach Besuchen an Hunden mit Darmfisteln, Centralbl. f. klin. Med. **14**:377, 1893.

28. Serdjukow: Abstr., Jahrb. ü. d. Fortschr. d. Physiol. **8**:214, 1899; Eine der wesentlichen Bedingungen des Durchganges der Speise aus dem Magen in dem Darm, Arbeiter der Gesellschaft russische Aertzte in St. Petersburg, August and October, 1899, p. 46.

29. Tobler: Ueber die Eiweissverdauung im Magen, Ztschr. f. physiol. Chem. **45**:185, 1905.

their experiments their work will be considered in some detail, and in the order named above, for I feel that their conclusions cannot be applied to the processes of normal digestion.

Some of Hirsch's work has already been outlined. He first showed that organic acids left the stomach slowly and that the higher the concentration, the slower the rate of exit. Although Hirsch stated that he did not believe that the reaction of the gastric contents had any influence on the opening or closing of the pylorus, nevertheless, his experiments are at times not so interpreted. Thus, it is believed that the increased strengths of acid require a longer time for neutralization in the duodenum and hence that the pylorus remains contracted for a longer interval. But surely Hirsch's experiments cannot be said to prove that. As Cannon confessed, they give no answer to the reason why the acids leave slowly—whether this was due to a disturbance in the peristalsis or to the closure of the pylorus. And since it has already been shown that by action on the duodenum there is a reflex slowing of gastric peristalsis and possibly a diminution in gastric tone, that may at least partially account for the slow discharge. Finally, as will again be emphasized, 0.3 per cent., 0.5 per cent. and 1 per cent. hydrochloric acid are not normal concentrations for the duodenum and do not occur there in normal digestion. Any conclusions drawn from their use apply to that strength of acid and not to the strength usually found.

As von Mering's [18] work is usually referred to in connection with the effect of mechanical stimulation on the intestine, I shall later return to it under that head.

Serdjukow's [28] experiments performed in Pawlow's laboratory have been widely mentioned as proof that acid in the duodenum prevents the exit of the gastric contents by keeping the pylorus shut. He poured into the duodenum of a dog with a gastric and duodenal fistula 5 c.c. of pure gastric juice (not gastric contents, which have a much lower acidity) from another dog. This gastric juice was shown to contain 0.52 per cent. hydrochloric acid. Two minutes later, 100 c.c. of 0.25 per cent. sodium bicarbonate solution was passed into the stomach; then every two minutes 5 c.c. of the gastric juice was poured into the duodenum through the fistula. After one and one-quarter hours 95 c.c. of alkaline fluid was still left in the stomach. The inference is that the acid in the duodenum kept the pylorus closed so that none of the gastric contents could emerge. In the first place, this method makes no differentiation between how much of the delay was due to the pylorus and how much to the peristalsis or lack of it in the stomach. Second, what is true of 0.52 per cent. hydrochloric acid need not necessarily be true of acid in the strength normally found in the duodenum. This strength is over twice that normally found even in the stomach contents, which is approximately 0.2 per cent. The subject will be more fully discussed presently.

But to emphasize once more, the conclusions drawn from Serdjukow's experiment cannot unreservedly be applied to the process of normal digestion, for the strength of the acid he used is far in excess of that which the gastric waves sweep over into the duodenum. And that is very fortunate, for otherwise our stomachs might never empty.

Tobler [29] had a dog with a duodenal fistula. Into the duodenum he inserted a balloon and distended this with air so that it would competely block the lumen below the fistula. But alongside the balloon he placed a catheter so that he could inject material through it into the duodenum below the balloon. The animal was fed 100 gm. of finely chopped meat. Spurts of fluid came from the duodenal fistula at intervals of from twelve to twenty seconds, which would correspond to from three to five peristaltic waves per minute. Then if he took the chyme which this dog had expelled through the duodenal fistula on the previous day and which had been preserved on ice, and injected some of it (he does not say how much) from every five to fifteen minutes into the catheter so that it passed into the duodenum below the balloon he obtained the following results:

After every injection there was a cessation of discharge through the duodenal fistula for from three to ten minutes; then the gushes from the fistula began to emerge every three minutes, later from every five to seven minutes, and finally from every ten to twelve minutes. He concludes that the action on the duodenum of the acid in the chyme injected through the catheter was responsible for the closure of the pylorus. The reason the food left so rapidly when the chyme had not been injected was because the acid had no time to stimulate the mucosa of the duodenum and permit it to close the pylorus reflexly. By inference we are therefore led to believe that the second set of results, that is, those in which the chyme was discharged at varying intervals of from three to twelve minutes, reflects the normal process of digestion. Yet such an inference surely is not warranted. In the first place, Tobler states that one must be very careful with the amount of pressure to which the duodenal balloon is distended, for a little too much is sufficient to abolish all discharge from the stomach for a short or longer interval. His injection then is very likely to upset this balance. The presence of such a balloon in the duodenum, which must be so finely adjusted as to pressure, surely places on such a method the burden of proof that the results are applicable to normal digestion. Then again he does not state how much chyme was injected each time through the catheter, and we cannot tell whether it approximated in quantity the amount that is ejected through the pylorus with each peristaltic wave. But folowing each of these injections the gushes from the stomach stopped for from three to ten minutes. (He says that the

pylorus closed, although such an inference could hardly be made with certainty, for there was no direct evidence to prove it.) Later these gushes emerged at intervals ranging from ten to twelve minutes. If we accept the evidence given above that every peristaltic wave forces chyme into the duodenum, we have further support to the belief that the unusual conditions under which Tobler did his work gave him these exceedingly long intervals. For even Cannon [1] (p. 60), who believed that the discharge through the pylorus was at irregular intervals, gives their usual limits as from ten to eighty seconds. There is no other evidence that each discharge of gastric contents into the duodenum is normally followed by an interval of from three to ten minutes. And so Tobler's work, too, cannot be said to prove that acid in the quantities normally found in the duodenum produces a closure of the pylorus and thus regulates the emptying of the stomach.

We may say then of this work that strong acids introduced into the duodenum delay gastric emptying. And this is in entire accord with the work already described showing that high acid concentrations in the stomach delay emptying and that the reflex for this delay is initiated in the duodenum after some of the acid is carried over. It will be remembered that some of the delay was due to slowing and weakening of the peristalsis. And even if at the same time there is a slight spasm of the pylorus in the foregoing experiments, it does not necessarily follow that the same is true when normal reactions and conditions are present.

But what is the usual reaction of hydrochloric acid in the upper part of the duodenum? The evidence seems to show that it is either alkaline or weakly acid. And that does not appear strange, for with an abundance of strong intestinal and pancreatic juices present in the intestine, the neutralization of the free hydrochloric acid carried over from the stomach must consume very little time. Thus, after feeding an animal, the examination of the fluid expelled through a duodenal fistula has in the hands of both Tobler [29] and Moritz [14] shown that this material contained no free hydrochloric acid. And in this country Luckhardt, Phillips and Carlson [8] similarly could demonstrate no free hydrochloric acid. Meyers and McClendon [30] ascertained that the hydrogen ion concentration of duodenal contents aspirated at the height of digestion ranged from p_H 3.8 to p_H 7.54. A hydrogen ion concentration of 3.8 is equivalent in terms of hydrochloric acid to a strength of approximately 0.0001 per cent. A hydrogen ion concentration of 7.0 represents neutrality. The reactions they found therefore varied from the acidity indicated above to a very weak alkalinity. Certainly

30. Meyers, F. J., and McClendon, J. F.: Note on the Hydrogen Ion Concentration of the Human Duodenum, J. Biol. Chem. **41**:187 (Feb.) 1920.

this strength in no way corresponds to the concentrations used in the experimental work outlined above, and from which conclusions were drawn as to the normal function of this sphincter. It will be remembered, for instance, that Serdjukow used 0.5 per cent. hydrochloric acid solution. We can therefore only conclude from his work that his results obtained for that strength of acid. And the whole would appear as a protective mechanism of the duodenum against high concentrations of acid.

It seems then that we must conclude that during the course of normal digestion, acidity on both the gastric and the duodenal side plays a small part, if any, in the opening and closing of the pylorus.

Summarizing then the effect of chemicals on the pylorus, we may say:

1. The presence of acid on the gastric side is not necessary for the opening of the pylorus.

2. Normal concentrations of acid on the duodenal side do not keep the pylorus closed.

3. Concentrations of acid higher than normal in the stomach cause a slowing of gastric peristalsis, and while this is especially notable in concentrated experimental solutions, it is however also noticeable within the limits found in hyperchlorhydria.

4. Very strong acids cause a complete inhibition of peristalsis, and even reverse peristalsis and vomiting.

5. The site of origin for this reflex is the duodenum.

6. The theory of acid control on both sides of the pylorus (Cannon) or from the duodenum alone does not explain all known facts.

B. EFFECT OF MECHANICAL STIMULI ON THE PYLORUS

Mechanical Stimulation on the Gastric Side.—It has been shown that the action of hydrochloric acid does not adequately explain the control of the sphincter of the pylorus during the course of normal digestion. That leaves as other possible factors thermal and mechanical stimuli. Since thermal stimuli (they will be considered later) must obviously be limited in their influence, mechanical stimulation is left for serious consideration. As in the previous section, the effect of stimulation on the gastric side of the pylorus will be considered first, and then the effect on the duodenal side.

That the contents of the antrum are normally fluid has long been known and conceded, and needs no special comment. Solids are fluidified in the body and fundus by means of ferments, and the constant pressure of these parts aided by the gentle peristalsis forces the fluid or pulpy portion over into the antrum. Here the strong muscular

action helps mechanically to squash the contents. The material forced over into the duodenum is normally fluid. Thus far all agree.

What occurs if perchance a solid portion of food has been carried into the antrum? In four of the dogs studied by me, retrograde peristaltic waves were seen to begin at the pylorus and run up to the reentrant angle, that is, through the entire course of the antrum and up to the body. These were repeated three, four or more times. In each case palpation of the antrum revealed the presence in it of either a bone or a large piece of meat. The peristaltic waves recurred until the solid body had been pushed back into the body of the stomach. In one dog a piece of meat and in another a small bone was pushed by me from the body into the antrum. The normal peristalsis which was going on till then immediately ceased, and retrograde waves commencing at the pylorus forced back the meat and the bone into the body. All these dogs were prepared in the manner previously described.[2] One-half hour before the observations, they received a meal of broth, meat and small bones totaling one-half liter.

These observations are in agreement with those of Hoffmeister and Schütz.[31] It will be remembered that their method was to excise the stomach of a dog and to place it in a moist chamber. Some of their dogs had been fed, others had been starved. Occasionally they saw waves commencing at a closed pylorus and running back to the level of the reentrant angle. As these waves were only seen in stomachs that contained coarse food, they concluded that some large particles had found their way into the antrum and were being driven back into the pylorus. They did not, however, actually feel these particles. Over one hundred years ago Magendi,[32] too, had reported that any solid bodies carried into the antrum were driven back into the body of the stomach. Von Pfungen [33] had later made a similar observation. Apparently, therefore, a mechanism exists to prevent (for a time at any rate) the passage of solid material into the intestine. That solids can pass over, however, is well known. But they seem to be limited for the most part to nondigestible material, and are probably carried over at the end of digestion when pyloric tone is lowest. On one occasion I followed the progress of a bone through the pylorus. It was a small elongated bone about 1½ inches long. Continuous systolic waves coursed over the stomach, and as each wave reached the bone it was pushed about one eighth of an inch onward. It took fifteen waves to push the bone

31. Hoffmeister and Schütz: Ueber die automatischen Bewegungen des Magens, Arch. f. exper. Path. u. Pharmakol. **20**:1, 1885.

32. Magendi quoted from Luciani: Physiologie des Menschen, Jena **2**:167, 1906.

33. Pfungen (Footnote 30, p. 162).

through the pylorus. During this time a portion of the bone was, of course, both in the stomach and in the duodenum.

It seems probable (although no work has been done to prove this) that the site for the stimulus of these retrograde waves is the pylorus. Apparently, when the solid particle is carried up against the sphincter the latter closes and retrograde waves which drive it backward are initiated.

This phenomenon is, no doubt, an exceptional occurrence. The influence of the degree of fluidity of the gastric contents on the emptying time of the stomach may, however, be of more importance. As a result of his observation on dogs by means of a duodenal fistula, Hirsch [27] first concluded that the fluidity of the stomach contents was one of the most important factors in gastric emptying, but his proofs seem inadequate. Later Moritz,[14] using the same method, reached the same conclusions. Working with water, milk and meat, he showed that pure fluids (water and uncoagulated milk) came out most rapidly; when the milk was coagulated, the rate of discharge was slower. The meat took longest of all to be discharged. Further, if fluid was given the dog while meat was in the stomach, the fluid was expelled rapidly, but the solid portions of meat were retained till either fluidified or changed to a soft pulpy consistency. Cohnheim,[34] also using a duodenal fistula, found that finely chopped meat began to leave the stomach in fifteen minutes, and that 50 gm. left the stomach in one hour and thirty-five minutes. If on the other hand, 50 gm. was fed to a dog in lumps from 1 to 2 cm. large, it took two hours and thirty minutes for the stomach to empty itself. More recently, Ortner [19] prepared a thick pulp of charcoal in water and diluted it to suspensions of varying fluid content. These different mixtures were fed to dogs with duodenal fistulas and the time recorded when the first material was discharged through the fistula. He found that the greater the water content, the earlier the discharge through the fistula. Incidentally, all the material discharged was neutral in reaction. He believed that his results spoke very strongly for the theory that fluidification, entirely apart from the reaction and the chemical composition, gave the stimulus for the opening of the pylorus. While that conclusion is entirely possible, it cannot be made with certainty because his method, as before stated, does not distinguish between delay due to the pylorus and that due to slowing of gastric peristalsis. Cannon,[35] too, in spite of the great importance he ascribed to the chemical control of the pylorus, believed that the addition of hard particles to the food caused delay in emptying.

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34. Cohnheim: Die Physiologie der Verdauung und Ernährung, Berlin, 1908, p. 22.

35. Cannon (Footnote 1, p. 122).

We may, therefore, say that the state of the material normally discharged through the pylorus is fluid; that a mechanism exists in the antrum or pylorus to hinder the exit of undigested (or unfluidified solids), and that it is probable that the higher the fluid content of the food in the stomach the more rapid its discharge. And in view of the previous discussion of the chemical control of the pylorus, these things are true regardless of the chemical reactions, provided they be within physiologic limits.

Effect on Pylorus of Mechanical Stimulation of the Duodenum.—The early experimental work to determine the effect on the pylorus of mechanical stimulation of the duodenum is open to the same two faults mentioned in connection with the inquiries concerning chemical control. Thus, first, stimuli were applied that do not occur during normal digestion, and, second, the method did not distinguish between delay due to closure of the pylorus and delay due to cessation of gastric peristalsis.

In 1893 Hirsch [27] first called attention to the following fact: If water was given by mouth in an animal with duodenal fistula, it flowed out through the fistula so rapidly that at the end of one-half hour the stomach was always empty. But if he now closed the duodenal fistula and so permitted all the water to pass into the intestine and then repeated the foregoing experiment, at the end of one-half hour appreciable quantities of fluid could still be aspirated from the stomach. And this was also true of an animal in which no fistula had been created. He concluded, therefore, that a reflex from the intestine regulates the emptying of the stomach; that when no duodenal fistula exists, the fluid remains to distend the intestine and a reflex regulates the further discharge. When on the other hand the fluid immediately passed out through the fistula this did not occur and rapid emptying resulted.

A few years later, von Mering [13] confirmed this. In addition he found that if a dog was given 400 c.c. of water by mouth and immediately following this 300 c.c. of milk was injected over a period of one hour into a duodenal fistula, at the end of the hour only 9 c.c. of fluid was discharged through the fistula, the rest being retained in the stomach. On the other hand, if nothing was injected into the fistula the stomach would be empty in twenty-five minutes. The latter work reminds us of a similar experiment of Serdjukow [28] with pure gastric juice (approximately 0.5 per cent. hydrochloric acid), and it is open to the same objections. The injection of ordinary milk in such a manner cannot be said to parallel the ejection of chyme from the stomach by the peristaltic waves. And this is conclusively shown by the fact that at the end of one hour only 9 c.c. of fluid had left the stomach. Then Mar-

baix [36] found that if long areas of intestine were filled with fluid through fistulas, the discharge from the stomach was inhibited. Here, again, as Cannon [37] points out the conditions are not normal for food is distributed in the intestine in separate short masses. Later Tobler,[29] as has already been stated, noticed that if a balloon were inflated in the duodenum, gastric discharge could be completely stopped.

None of these methods prove that the effect produced was really due to closure of the pylorus, although these observers seem to think that this was the cause of the delayed emptying rather than a disturbance of peristalsis. That strong mechanical stimulation of the duodenum does affect gastric peristalsis is shown by the observations of McClure, Reynolds and Schwartz.[5] During their experiments, previously referred to, they found that pulling back the tip of a duodenal tube from the second and third portion of the duodenum to the pylorus caused a cessation of gastric peristalsis, which lasted in one case one-half hour. These observations were made by means of the fluoroscope.

But strong mechanical stimulation also directly affects the pylorus. Thus, the vigorous mechanical stimulation incident to the introduction of an observation cannula into the duodenum through a duodenal fistula, in an attempt to observe the pylorus, resulted in long continued pylorospasm and vomiting.[8] And in agreement with the work of other authors, Wheelon and Thomas [38] found that an attempt to palpate the lumen of the pylorus with one finger, through a gastric fistula, always led to a firm pylorospasm.

We may say, then, as a result of the foregoing experiments: First, that just as strong chemical stimuli cause delay in gastric emptying, so do powerful mechanical stimuli; second, that this delay is probably due either to closure of the pylorus or to cessation of gastric peristalsis, or both, and it seems natural that these two factors should work together; and third, that such potent mechanical stimuli applied as described above unquestionably have these effects, but that they do not operate under normal circumstances.

One set of observations, however, seems to have an important bearing on normal digestion. That is the work of Hirsch [27] and of von Mering [13] mentioned above in which each showed that the stomach emptied itself more rapidly in dogs in the presence of a duodenal fistula. When the chyme is forced through the pylorus it is passed into the first portion of the duodenum, commonly called the "bulb." This portion acts as a temporary reservoir and its walls are distended by the chyme. When a high duodenal fistula has been performed, the chyme immedi-

36. Marbaix: Le Passage Pylorique, La Cellule **14**:251, 1898.

37. Cannon (Footnote 1, p. 97).

38. Wheelon, H., and Thomas, J. E.: Rhythmicity of the Pyloric Sphincter, Am. J. Physiol. **54**:460 (Jan.) 1921.

ately passes out through this and no distention of the first part of the duodenum takes place. It seems possible that distention has some influence on the emptying time of the stomach. But whether the reflex effect is exerted on the rate and strength of gastric peristalsis or on the tone of the pylorus, or on both, cannot be stated from the foregoing experiments. We can only say that when the distention occurs the rate of discharge is slower than when it is absent.

In view of the foregoing observations, we may now summarize the effect of mechanical stimuli as follows: If there is material of a fluid or pulpy consistency in the stomach, it is forced into the antrum by the tonus of the fundus and body and by the light peristaltic waves of the latter. Every advancing peristaltic wave in the antrum then forces some of this chyme into the duodenum. During the early part of digestion, if a solid piece of food finds its way into the antrum, it is carried back to the body by retrograde peristalsis. During the latter part of digestion, the consistency of the expressed material seems to be thicker, and solid (usually undigestible) substances may be forced through. Further, the chyme is propelled through the pylorus whether its reaction is acid, neutral or alkaline (provided these reactions be within physiologic limits). Strong mechanical stimuli in the duodenum, more marked than those occurring during digestion, unquestionably delay or abolish gastric motility by closure of the pylorus or inhibition of peristalsis or both. But normal stimuli incident to the distention of the duodenal bulb by the chyme may regulate in part the gastric emptying. Whether that effect is on the tone of the pylorus or on the gastric peristalsis, the foregoing researches do not make clear.

C. EFFECT OF TEMPERATURE ON THE PYLORUS

The reported effects of temperature on gastric emptying time are somewhat contradictory. Thus, Müller [39] found that fluids at body temperature left the stomach most rapidly, while those that were hot or cold left more slowly. Roeder's [40] results were exactly opposite, the solutions at body temperature being the slowest to leave. It would be exceedingly interesting to determine definitely the effect of temperatures on the tone of the pylorus and on gastric peristalsis. Nevertheless, this effect cannot be of vast importance in the process of normal digestion. For the stomach rapidly brings to body level the temperature of the food that is taken, and any stimulus that would exist because of a variation

39. Müller: Ueber den Einfluss der Temperatur der Speisen auf die Magenfunktionen, Ztschr. f. diätet. u. physik. Therap. **8**:587, 1904.

40. Roeder: Ein Beitrag zur Lehre von der Motilität des Magens, Med. Klin. **22**:816, 1909.

from that level would at the same time disappear. Quincke,[41] for instance, found that water of 40 degrees C. reached body temperature in the stomach in ten minutes.

D. PROBABLE MANNER OF CONTROL OF THE PYLORUS

We shall now pause for a moment to reconsider the questions that have been discussed. We started with an assumption which practically all will accept, namely, that the pylorus is closed following the ingestion of food into the stomach. Then Cannon's theory, the first part of which assumed that acid on the gastric side was necessary to open it, was considered. It was shown, however, that the absence of acid did not prevent the food from leaving, and hence that acid was not necessary for the opening of the pylorus. The second part of the theory was then considered, which like the Hirsch-von Mering theory assumed that acid on the duodenal side controlled the pylorus, the sphincter remaining closed as long as acid was present there, and opening as soon as the acid was neutralized. This theory was likewise found wanting for it would imply that if no acid were present in the duodenum the pylorus would remain continuously open. This is not so, for the pylorus closes in the absence of acid. Further, it was shown that food could leave the stomach even while the reaction in the duodenum was acid. Hence this theory, too, is unsatisfactory. Next, the mechanical theory of regulation from the duodenum was considered. It was found that distention of the duodenum influences the rate of emptying. But no evidence was adduced that in the amounts normally present it controlled the opening and closure of the pylorus. It is possible to believe that distention of the duodenum by the chyme effects the closure of the pylorus, and that its relaxation permits opening. But that has not been proved. And in addition the experiments of Wheelon and Thomas,[9] already described, showed that the pyloric closure occupies a fixed relation to antral contraction. Evidence presently to be described also tends to show that the peristalsis of the antrum is intimately bound up with the closure of the pylorus, too closely to permit of the belief (just as Wheelon and Thomas found with acids) that mechanical stimulation from the duodenum could effect closure of the pylorus without first acting on the antrum. Nevertheless, it may be that mechanical stimulation of the duodenum influences the tone of the pylorus in the manner to be described later. We may say then that thus far none of the theories are consistent with the facts as we believe them.

When I described in a previous section the character of the peristaltic waves in the dogs I studied,[2] nothing was stated concerning the pylorus.

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41. Quincke: Ueber Temperatur und Warmeausgleich im Magen, Arch. f. exper. Path. u. Pharmakol. **25**:375, 1888, cited by Cannon (Footnote 1, p. 125).

The same technic that has been described was used. Three sets of observations seem of great importance. First, contraction and relaxation of the pylorus could easily be differentiated. In the former, the muscle was firmly contracted, markedly anemic and white in color. To the touch it was as hard as cartilage. There was no doubt that the lumen was totally obliterated. In the latter, the musculature was definitely relaxed; the color of the musculature was the same pink as that of the relaxed stomach, and the pylorus felt soft. While of course the pyloric lumen could not be visualized, there seemed but little question that it was patent. And that belief was further substantiated by the fact that in some dogs during the entire period of relaxation fluid could be heard and felt being forced through the pylorus. Furthermore, if the pylorus was grasped between the thumb and the forefinger with the one on the gastric and the other on the duodenal side, a lumen of variable size could be felt.

The second fact of importance was the relation of these stages of contraction and relaxation to the gastric peristaltic wave. During normal peristalsis, the contraction occurred only after the peristaltic wave had reached the pylorus. After a regular interval (presently to be considered) the relaxation followed. When no waves were present in the antrum, the pylorus was relaxed. This does not mean that chyme necessarily was passing through, for food does not leave the stomach unless it is pushed out. If Cannon't theory were correct, the pylorus would have been contracted most of the time, and the relaxations would have occurred independently of the peristaltic waves; but, as stated above, unless a peristaltic wave had passed down to the pylorus it remained relaxed. Contraction (except in retrograde peristalsis) did not occur independently of these waves. It was always their culmination.

The third important factor was the time relation of contraction and relaxation. In dogs with four waves to the minute the average length of the contraction, as measured by a stop watch, was from four to five seconds and the average length of the stage of relaxation was from ten to eleven seconds. In other words, the pylorus was firmly closed for from but one quarter to one third of the gastric cycle. For the remainder of the time it was relaxed. That is hardly in agreement with the conception that the pylorus is closed for the larger part of the cycle and opens at intervals to let the food through. It would appear more correct to conceive the pylorus as patent to permit the passage of chyme and closing at regular intervals after each discharge into the duodenum.

These factors lead to the following conception of some of the mechanical conditions incident to digestion. Following the entrance of food into the stomach, the pylorus, which has been relaxed, assumes a state of tone. That is what has usually been referred to as the closure

of the pylorus. Of course, if a circular ring of muscle becomes moderately tonic, and there is nothing within its lumen, its margins will be in contact. In that sense the pylorus may be said to be closed. But normally that state of tone is less than the pressure to which the fluid contents of the antrum are subjected by the advancing peristaltic wave. And so this wave during its progress through the antrum partially overcomes the closure and forces chyme in a continuous stream through the ringlike opening of the pylorus. The size of this ring will depend on the amount of tone of the pylorus on the one hand, and on the pressure created by the peristalsis on the other. During the larger part of the gastric cycle then the pylorus is open, and chyme is being forced through it. It is difficult to say where the tone stimulus to the pylorus arises. But it seems probable that it usually comes after some of the fluid has been passed into the duodenum. Naturally, the amount of tone in the pylorus may vary, but the factors that bring this about have not altogether been determined. We have seen, for instance, that unnatural stimuli, such as strong mechanical irritation, may cause a firm spasm, and this factor may have aided in the slower exit of the strong acids used in some of the experiments outlined above. Also, in normal digestion the acidity and mechanical state of the chyme vary, and they may alter the amount of tone, but the normal stimuli do not cause spasm. It also seems probable that extrinsic impulses through the vagi and sympathetics may vary the amount of the pyloric tone. This is one phase of the activity of the pylorus.

The other phase is closely related to the peristaltic wave. As the peristaltic wave advances down the antrum, its ringlike contraction becomes deeper and deeper until it finally reaches the pylorus. The latter is then contracted to the intensely hard white structure mentioned above. As already stated, the length of this contraction is from one third to one quarter of the cycle. This closure is of a different type from the one described above. Nothing can pass through the pylorus when it takes place. Whether the length of this closure may be influenced by local or distant stimuli, I cannot say. But it appears from watching the waves that the length of the contraction is dependent rather on the rate of peristalsis, and that it consumes a more or less fixed relation to the time of the entire wave. It will also be evident that this firm closure occurs when the pressure in the antrum is lowest (when the advancing wave has reached the pylorus) and when it effectually prevents regurgitation of chyme from the distended duodenal cap.

I would again emphasize, in the first place, the pyloric tone, which the pressure of the chyme in the antrum opens to a diaphragm-like lumen during the larger part of the time, and, second, the firm contractions at the end of the peristaltic waves, alternating with relaxations. If there are no peristaltic waves, these firm contractions do not normally

occur. Under those conditions, if the pressure exerted by the tonicity of the stomach is sufficient to overcome the tone of the pylorus (which may be very low or high, depending on the nature of the foodstuffs and other causes), material may be forced into the duodenum without peristalsis. And on the other hand, if the pressure in the duodenum is greater than the tone of the pylorus and greater than that existing at that particular time in the stomach, then the duodenal contents may be forced back into the stomach. As has already been indicated, the amount of tone of the pyloric sphincter varies during digestion.

The conception that the pylorus remains firmly contracted and opens at intervals not related to the peristaltic waves is, as has already been stated, contrary to the conditions observed. Nor does the theory that the pylorus is firmly closed and opens just before each wave reaches it to permit the passage of chyme, and then directly closes again, accord with the phenomena seen. Further, there are many experimental observations that would tend to confirm the view I have just outlined.

Among these may first be mentioned the work of Boldyreff.[42] Pawlow [43] showed that the strength of the gastric juice as secreted by the glands varied from 0.35 to 0.5 per cent. hydrochloric acid solution. Innumerable observations have confirmed these findings, which are, of course, much higher than those of the acidity of the gastric juice, which ranges between 0.15 and 0.2 per cent. hydrochloric acid solution. How is the reduction in acidity effected? That other factors than dilution by the food or combination with the protein also were at work was shown when a solution of 0.5 per cent. hydrochloric acid was placed in the stomach through a fistula and found after a time to be reduced to an acidity of from 0.15 to 0.2 per cent. hydrochloric acid solution. Evidently, some of the alkaline fluids of the organism had accomplished that. Those that may have brought about this result were the saliva, the bile, the intestinal juice, the pancreatic juice, and an alkaline secretion from the stomach itself. Boldyreff excluded each of these in turn. He then found that the one secretion that was indispensable to proper neutralization was the pancreatic juice. And he concluded that the regurgitation of the latter by retrograde peristalsis brought about the foregoing result.

Boldyreff's conclusion, namely, the regurgitation of pancreatic juice and incidentally of bile into the stomach as a normal occurrence of digestion when the neutralization of acid is necessary, has been confirmed and accepted by many representative workers. Among them may be

42. Boldyreff: The Self Regulation of the Acidity of the Gastric Contents and the Real Acidity of the Gastric Juice, Quart. J. Exper. Physiol. **8**:1, 1914.

43. Pawlow: The Work of the Digestive Glands, translation by W. H. Thompson, London, 1910.

mentioned the following: Hicks and Visher [44] in Carlson's laboratory, using bile as an indicator of intestinal regurgitation (although pancreatic juice may be regurgitated without bile), found that bile was present in the stomach in from 30 to 40 per cent. of the cases. Spencer, Meyer, Rehfuss and Hawk,[18] working with men who had swallowed a Rehfuss tube, found that if 0.5 per cent. hydrochloric acid solution was introduced into the stomach and samples aspirated through the tube every twenty minutes, the acidity was rapidly reduced, and that as it went down the tryptic values increased. After water was given by mouth, trypsin was found to be present in all aspirated specimens and nearly all contained bile. After a small Ewald meal trypsin was nearly always found to be present. They concluded that regurgitation of the duodenal contents into the stomach is a response to irritation of the duodenum and part of an attempt to render harmless substances that would have an injurious effect on the small intestine. They believe that this phenomenon is a constant accompaniment of gastric digestion. Deutsch and Rürup [45] recently came to similar conclusions from their studies on forty people. Gross [46] studied a boy in whom there was an esophageal fistula preventing all saliva from reaching the stomach. The boy was fed through a gastrostomy. Pancreatic ferment could be demonstrated in the stomach at the height of digestion, indicating, of course, pancreatic regurgitation. Morse [20] reached similar conclusions with animal experiments.

We may then say with some certainty that duodenal regurgitation is a common occurrence during digestion. If now the pylorus remains tightly contracted, and opens only just before the antral wave reaches it, it is difficult to see how any regurgitation could occur. For it would have to take place against the stream of chyme and at a time when the pressure in the antrum was at its highest. If on the other hand, pyloric tone is moderate or low, retrograde peristalsis or some other form of pressure in the duodenum could easily force over some of the duodenal ferments. This would most likely occur when the pressure on the gastric side was relatively low, that is, either when peristalsis was for a time in abeyance or when the peristaltic wave was quite distant from the pylorus. The firm closure of the pylorus occurs, as was stated, at the termination of the gastric wave.

We shall next consider the work of Cole.[4] It seems hardly to have received the attention due it. He took serial roentgenograms of a large

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44. Hicks and Visher: The Mechanism of the Regurgitation of Duodenal Contents into the Stomach, Am. J. Physiol. **39**:1, 1915.

45. Deutsch and Rürup: Ueber den Rückfluss von Pankreassaft in den Magen und die Bestimmung der Salzsaurerestenz des Trypsins, Deutsch. Arch. f. klin. Med. **138**:165, 1922.

46. Gross, O.: Ueber der physiologischer Rückfluss von Pankreassaft in den Magen, Deutsch. Arch. f. klin. Med. **132**:121 (April) 1920.

number of persons at short intervals which placed side by side make almost a moving-picture of the stomach in action. His description of the gastric peristalsis has been outlined above. What concerns us here is that his pictures show that for seven tenths of the gastric cycle the pylorus is open and chyme is being expelled through it. For the remaining three tenths the pylorus is shut. He found, too, that the tone of the pyloric sphincter was greatest during the earliest part of digestion and grew progressively less to the end. The figures mentioned in my experiments, namely, that the pylorus was relaxed for about three fourths of the gastric cycle, agree very closely with those of Cole. Evidently during digestion, when the peristaltic waves are coursing over the stomach, the pylorus is open more of the time than it is shut.

Another group of experiments that may be mentioned are those of Wheelon and Thomas.[38] Through an incision in the stomach they inserted a small specially constructed balloon into the pylorus. They used three types. In two of these the pyloric lumen was totally occluded, while in the third a central channel through the balloon permitted the passage of material from the stomach into the intestine. The contractions of the pylorus transmitted by these "pylorographs" were recorded on a drum. They found, after any initial disturbances due to handling had subsided, that there were regularly recurrent waves of contraction, relaxation and quiescence. In one case a roentgenogram was taken at the height of contraction and showed that at that time the pylorus was tightly contracted. Evidently then the summit of each wave is synchronous with pyloric contraction and closure. The time consumed by the contraction averaged from four to five seconds, the relaxation from three to seven seconds, and the quiescent period ranged from five to eight seconds. This makes the duration of a cycle from twelve to twenty seconds. If we remember that the period of contraction was from four to five seconds, this means from one third to one fourth of the cycle and would agree with the figures quoted above. Other exceedingly interesting observations are that the normal tonicity is only sufficient to close the sphincter or to approximate its surfaces against those of a body in the lumen. If that is so it is very logical to assume that any marked increase of pressure on either side, such as occurs with an advancing peristaltic wave, will be sufficient to overcome that tone and to permit the passage of fluid contents. The size of the diaphragm-like opening in the pylorus will depend on the relation between the amount of pressure in the antrum and the amount of tone in the pylorus. And the time of opening also will vary with the relative pressure, so that with a relatively higher tone in the pylorus the moment that the pylorus gives way will be at a later time in the gastric cycle. In that case the open state would be for a shorter length of time. In spite of this, it would appear from the

observations first mentioned and from the rest of the evidence that has been detailed that during periods of peristalsis the pylorus is open for a longer interval than it is closed.

One further set of observations remains to be mentioned. They are those of Luckhardt, Phillips and Carlson.[8] They performed a duodenostomy and a gastrostomy on their dogs. They introduced a balloon connected to a recording apparatus into the stomach. Either water, an acidified starch paste or a milk peptone mixture also was put into the stomach. A tube was then passed into the duodenostomy opening so that its opening was close to the pylorus. As each drop issued from the tube, it was registered under the tracing of the balloon by a signal magnet. These tracings showed that "the drops issued most abundantly when the constricting ring had reached the pylorus." But the authors do not, it appears to me, emphasize sufficiently that this was not the only time that drops emerged. Their tracings show that as the pressure was rising, that is, as the wave was approaching the pylorus, there also was a discharge of drops. In other words, the pylorus must have been open not only when the constricting ring was close to the pylorus, but also during part of the time it was traveling through the antrum. They further show that gastric contents may pass out through the pylorus in the absence of gastric peristalsis, and owing to a general increase in tonic activity of the musculature as a whole. This is in entire accord with the conception I have postulated, and probably occurs at a time when the pyloric tone is low.

A possible objection that may be advanced is that this patency is not more evident under fluoroscopic examination. I am sure that careful examinations of roentgenograms will very frequently show the patency of the pylorus in the presence of an advancing peristaltic wave in the antrum. And where no shadow is seen at the site of the pylorus, one cannot say that the lumen is closed. I quote from Schlesinger.[47]

> It may be very difficult to determine whether the pylorus is open or closed. The observations are made difficult because of the fact that at times only small amounts are expressed which do not cast a visible shadow, or the material expressed may be so completely mixed with substances that permit the roentgen rays to pass through, that even with more profuse emptying no visible shadow arises. The pylorus then appears to be closed when in reality it is open.

In view of these facts, we can see that the problem which confronts us is not so much a study of the factors that are responsible for the opening and closing of the pylorus as a study of the phenomena that influence the gastric emptying time. If pressed for an answer to the

47. Schlesinger, E.: Die Röentgendiagnostik der Magen und Darmkrankheiten, Ed. 2, Berlin, 1922, p. 80.

first question alone, we would have to say that the pylorus is opened by the increased pressure of the antrum transmitted to the sphincter by its fluid contents, and that the pylorus may be closed in two ways: first, by the approximation of its walls by the tone of the sphincter (which, of course varies in amount) if at the time the pressure on either side is insufficient to overcome this tone, and, second, by the firm contraction that occurs when the peristaltic wave reaches the pylorus.

But since the problem seems to be one largely of pressure relations, we cannot wholly dissociate the behavior of the pylorus from gastric peristalsis and tone. Given the same degree of resistance (that is, the tone of the pyloric sphincter) and a strong propulsive force (that is, the tone of the stomach and the rate and strength of the gastric peristalsis), we will have much more rapid emptying than with the same resistance and a weak propulsive force. The total absence of resistance (a wide open pylorus) will not aid the emptying unless the propulsive force is adequate. On the other hand, the most vigorous peristaltic waves will have great difficulty in overcoming a firm pylorospasm. But under the usual conditions of digestion, the resistance (that is, the tone of the sphincter) is merely sufficient to allow with the increase of pressure in the antrum the passage of a narrow stream of fluid chyme into the intestine, be the reaction of this chyme what it may within normal (nonirritating) limits. The tone of the pylorus exists for that purpose. Normally it only accomplishes the closure of the sphincter when the pressure on the antral or duodenal side is insufficient to overcome it. The decisive closure in the regular cycle of digestion is effected when the peristaltic wave has reached the pylorus. That closure prevents the backward passage of fluid contents from the distended duodenal cap. Studies on the pylorus must distinguish between the effects due to each of these two distinct phases: first, the tone of the sphincter, and second, the gastric cycle consisting of the peristaltic wave and its culmination at the pylorus, producing the closure of that sphincter. This conception is not open to the objections advanced against the other theories, and it is consistent with the known facts of gastric motility and digestion.

CONCLUSIONS

1. Acidity on the gastric or duodenal side of the pylorus does not normally control the activity of that sphincter.

2. Fluidity of the chyme in the antrum is the factor of prime importance for its expression.

3. Solid bodies which by chance get into the antrum are carried back into the body by retrograde peristalsis.

4. Each advancing peristaltic wave overcomes the tone of the pylorus and forces some of the chyme into the duodenum, regardless of whether the reaction of the chyme is neutral, acid or alkaline.

5. The period of expression of the chyme during which the pylorus is open occupies a greater part of the gastric cycle than the period in which it is closed; in other words, the pylorus is open for a longer time than it is closed.

6. The pyloric tone normally only keeps the sphincter closed when the pressure on either side is insufficient to overcome it. This is one type of pyloric closure. It is overcome, on the one hand, by each advancing gastric wave, and on the other, may be overcome by retrograde peristalsis in the duodenum resulting in intestinal regurgitation.

7. Firm decisive closure of the pylorus occurs at the termination of each peristaltic wave when the latter has reached the sphincter and after it has forced the chyme into the duodenum. It effectually prevents any regurgitation. The latter closure always occupies the same proportion of time in the gastric cycle.

8. Studies on the pylorus should differentiate between these two types of closure.

TWENTY-NINTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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(Continued from Page 1104)

BONE AND JOINT SURGERY

Joint Transplantation and Arthroplasty.—Lexer,[35] in a carefully prepared and well illustrated article, reports the results of his operations of joint transplantation and of arthroplasty, and discusses the relative merits of the two procedures in the light of the experimental and clinical evidence. Reestablishment of joint function comprises both the restoration of movement and the ability to bear weight. The choice of the operative procedure, therefore, depends on whether the problem is one of repairing defects of the joint region or of doing away with ankylosis. Joint transplantation is essential for the repair of a large defect of the joint, and in addition may have a place in the treatment of ankylosis. From his own experience and that of others, Lexer believes that the half joint transplantation operation, with either autoplastic or homoplastic material, offers the hope of reestablishing function even when there is a large defect, and that it should take the place of mutilating operations and of amputation. Discussing the matter of whether or not the joint capsule should be transplanted along with the joint, he states that his experiments with animals do not permit him to draw definite conclusions. However, from his clinical observations he doubts if the entire joint, enclosed in its capsule, can be satisfactorily transplanted. He has performed joint transplantation in twenty-three cases, of which eight were failures. In five of these there was recurrence of the tuberculosis or osteomyelitis. Of the twelve cases permanently healed, eight have been followed for several years, and all show good motion and weight bearing. The first attempts were made in cases of broad joint ankylosis, but he now feels that the operative procedures for the mobilization of stiffened joints, which in the meantime have been developed

35. Lexer, E.: Surg. Gynec. Obst. **40**:782 (June) 1925.

either with pedicled or free tissue interpositions, are more constantly successful and approach the goal more closely, since they are not dependent on homoplastic material, which is difficult to obtain. In the matter of after-treatment he would now advise the restriction of weight bearing by the use of a splint for a period of two years. He concludes that the number of cases suitable for joint transplantation is very limited. His opinion in this respect has been much influenced by the brilliant results which he has seen following arthroplasty. The operation must be planned in such a way as to steer between two dangers: on the one hand a loose, unstable joint, and on the other, recurrence of the ankylosis. He considers the after-treatment of fully as much importance as the operation. The careful selection of patients and the details of after-treatment are all the subjects of detailed discussion. Out of a total of 300 arthroplastic operations on large joints the results are stated to be good in 242, doubtful in twenty-four, and failures in thirty-four.

[Ed. Note.—Lexer's experiments with joint transplantation are well known and it is a matter of considerable interest to learn the results after a period of years in the human cases. These are presented in great detail, with early and late roentgenograms and with photographs, occasionally cinematic, to show function. The late roentgenograms of all the successful cases show an excessive amount of degenerative reaction with extensive marginal lipping and other evidence of faulty articular function. Obviously, the results have not been of a kind to warrant the general use of the procedure, a conclusion that finds support in Lexer's obvious lack of enthusiasm for the operation and his preference for arthroplasty. Nevertheless, he appears to have proved that it is possible to transplant half a joint from a homeoplastic source, and that in about half the cases this transplant may be expected to preserve its form and a considerable amount of its function. This alone is of considerable importance and a matter for which Lexer is entitled to congratulation. That these proofs are of greater scientific than practical interest is natural at present, but continued investigations may yield results of real clinical value.]

Arthroplasty.—Campell,[36] discussing the reconstruction of ankylosed joints by arthroplasty, states that with improvement in operative technic and greater care in after-treatment the results have been greatly improved. He estimates the chances for successful results as 90 per cent for the temporomaxillary joint, 90 per cent for the elbow, 60 per cent for a single hip, and 75 per cent for the knee. While believing that there is a great difference between arthroplasty and excision, he feels that surgical procedures should be directed toward reproducing function and not mere anatomic detail, thus simplifying and standardizing opera-

36. Campbell, W. C.: M. J. & Rec. **122**:255 (Sept. 2) 1925.

tive technic. There is little danger of the removal of too much bone so long as one remains within the bounds of reason. Unstable joints result from atrophy rather than from the amount of bone excised. The after-treatment must be intelligently carried out, especially with reference to osteoporosis or atrophic bone changes, which can be avoided by intensive physiotherapy and gradual weight bearing restricted by special apparatus. Campbell has worked out a type of brace for each joint, and lays special stress on the need for support along with proper physiotherapy. The late roentgenograms show extensive proliferative reaction about the margins of the articular surfaces. He does not consider this a true infectious arthritis, but rather in the nature of a reaction to trauma.

Spastic Contracture of the Wrist.—Wreden [37] advises a modified Stoffel operation for severe spastic contractures of the wrist. He disregards the special anatomy of the nerve fibers and simply excises, from both the ulnar and median nerves, about half the thickness of the nerves for a distance of 5 or 6 mm. In his experience it has been possible to extend the wrist to midposition immediately following the operation and gradually to obtain hyperextension. At the end of two weeks a certain amount of active flexion has been restored, sufficient for better use. In a case examined three years after operation, the contracture had been noticeably relieved and the active mobility greatly increased, and Wreden believes that further improvement may still be expected.

Subacromial Bursitis.—Carnett [38] reports his experience with a group of cases of subacromial bursitis associated with calcareous deposits, and endorses most of Codman's observations. Nineteen of his patients were treated by operation, with removal of the deposit. He considers stereoscopic roentgenograms essential in order to visualize and localize the deposits, which are never in the bursa but are beneath it. Following operation, a rubber drain is inserted for twenty-four hours, and the arm is fixed in moderate abduction by a sling and pillow. Voluntary and passive movements are encouraged after the first few days, but there is a special warning against forcible manipulation. The mere presence of a calcified area is not of itself an indication for operation, but if there is acute agonizing pain, the removal of the deposit affords the most prompt and certain method of relief and cure. Most of his chronic cases were operated on during an acute exacerbation of symptoms. He considers physiotherapy to be helpful in many chronic cases, but vigorous massage or manipulation merely increases the pain. Baking gives relief, but the author has seen no satisfactory results from diathermy. Permanent improvement depends to a great extent on the persistence of the patient in obtaining and maintaining normal use of the shoulder.

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37. Wreden, R. R.: Zentralbl. f. Chir. **52**:2155, 1925.
38. Carnett, J. B.: Surg. Gynec. Obst. **41**:404 (Oct.) 1925.

Bone Plastic Operations on the Hip.—Albee [39] describes the operative procedures that he has developed for use in various pathologic conditions of the hip. For ununited fracture of the neck of the femur he employs a method that is similar to the reconstruction operation described by Whitman, except that he splits the top of the femoral shaft and fractures the trochanter outward, instead of transplanting it downward, as in the former procedure. In irreducible congenital dislocation of the hip he builds out a shell from the ilium by turning down a flap from the latter bone and wedging in a bone graft on the upper surface to make the shelf secure. For arthrodesis of the hip he employs an extra-articular method, inserting two long bone transplants in the top of the trochanter and wedging their upper ends into the ilium. He shows the roentgenograms of one case eight years after operation in which the transplants have remained in place and increased in size.

Cysts of Iliopsoas Bursa.—Gatch and Green [40] believe that cysts as well as inflammatory conditions of the iliopsoas bursa are probably more common than the rather infrequent published reports would indicate. They have been able to collect only thirty-two cases of bursal involvement from the literature, of which twenty-two were cysts. Usually there is but little interference with mobility at the hip except that which results from the mechanical interference of the tumor. The tumor mass first makes its appearance in the upper part of Scarpa's triangle, immediately below the inguinal ligament at about its midpoint. Fluctuation may be detected when the hip is flexed, but is absent when it is extended. Durville points out that the pain caused by the tumor is readily explained by the intimate relation of the anterior crural nerve to the tumor mass. The tumor increases in size gradually and may reach the size of an infant's head. All writers agree that the only satisfactory treatment is excision of the cyst. In the case reported by the authors this was readily accomplished by an incision parallel to and just below Poupart's ligament.

Genu Valgum.—Reschke [41] reports the case of a boy, aged 10 years, with severe double genu valgum. He inserted small ivory pegs in the lateral portions of the epiphyseal cartilages of the lower end of the femur and of the upper end of the tibia. Within two years and without any other treatment both legs grew straight, the boy in the meantime doing full work as a farm hand. Reschke recalls a case demonstrated by Schueler in 1889 in which similar treatment had been successfully employed. In that case steel nails were introduced but were removed at the end of five days.

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39. Albee, F. H.: J. A. M. A. **85**:1345 (Oct. 31) 1925.
40. Gatch, W. D., and Green, W. T.: Ann. Surg. **82**:277 (Aug.) 1925.
41. Reschke, K.: Arch. f. klin. Chir. **138**:65, 1925.

Hemangioma of the Knee Joint.—O'Ferrall [42] has made a study of hemangioma of the knee joint based on a clinical experience with three cases. The differential diagnosis is difficult. The cardinal points are (*a*) history of the existence of a questionable tumor since early life or associated with more or less recent trauma; (*b*) the presence of an unusually sensitive mass in the joint, which is soft and slightly movable; (*c*) reduction in the size of the mass on elevation of the extremity; (*d*) pain of moderate degree associated with slight limitation of motion, and (*e*) negative roentgen-ray examination. The author feels that unless the possibility of hemangioma can be definitely ruled out, operative procedures should be deferred. This warning is given because of the difficulties that may follow from open intervention unless preceded by adequate roentgen-ray and radium treatment. The condition is most frequently encountered in children and young adults.

[ED. NOTE.—We agree that a course of radium or roentgen-ray therapy would be desirable as a preliminary to operative treatment, but in the majority of these cases the diagnosis can only be made at operation and then it would seem best to proceed with as complete an extirpation of the tumor as possible. In two cases treated by one of us this procedure was carried out with satisfactory results, and the patients have remained well.]

FRACTURES

The Fracture Committee of the American College of Surgeons.—Scudder,[43] describing the work of the Fracture Committee of the American College of Surgeons, states that it represents the organized effort of the medical profession to rectify the chaos existing in fracture treatment today. That over 60 per cent of all malpractice suits in the various states are for malpractice in fractures connotes the general woful backwardness of this phase of surgery. The unhappy state of fracture cases unwisely and inadequately treated, which have never come to trial but which every surgeon doing fracture work has seen, are too well remembered to call for further comment. Furthermore, end-result studies from certain clinics invariably show short periods of disability and high restoration of function while other clinics show consistently deplorable economic losses in their end-result surveys. The general desire for stabilization of fracture treatment and for greater skill in dealing with fractures resulted in the establishment by the college of the original Fracture Committee. With the work of this committee all are familiar. The Fracture Committee has since accomplished the introduction of a sixth requirement for all hospitals recognized by the college; namely, a minimum of equipment to care for the emergency treatment

42. O'Ferrall, J. T.: J. A. M. A. **85**:505 (Aug. 15) 1925.
43. Scudder, C. L.: Boston M. & S. J., Nov. 12, 1925, p. 911.

of fractures. The committee has prepared and the college is advising a special sheet for fracture records in these hospitals. Contact is being established in each of the approved hospitals throughout the country with a surgeon who is being held responsible to the committee for certain general details essential to proper fracture care, the recording of fractures, and for the securing of end-result records. Educational work has been undertaken in connection with better undergraduate instruction in fractures in the medical schools, and clinical demonstration of fracture methods with discussion of these under the auspices of a member of the committee have been established in Philadelphia, New York, Boston, Pittsburgh and Chicago. These are proving helpful to the profession at large.

Active Motion in the Treatment of Fractures.—Yates and Stevens [44] feel that one of the chief requirements in fracture treatment is to curtail the degree and duration of immobilization and to aid in every way the natural resources of the body in the healing of fractures. To this end those procedures ought to be selected which will interfere the least with general and local activities and which will permit the earliest resumption of unrestricted activity. Reapposition should be secured with the minimum trauma. If impaction is present and the position of the fragments is compatible with recovery of function; if reapposition of the fragments is useless or impossible, or if the fracture is incomplete, one should not interfere. They consider fair apposition obtained immediately by closed manipulation or presently by traction as usually preferable to more exact reapposition by the open method. Many impacted fractures and some well apposed nonimpacted fractures require no fixation and exceptionally may require no support. The less fixation and support employed beyond the requirements for safety, the more perfect the repair. Evidence is presented to show that bone repair occurs more promptly if active motion is employed and to prove that cooperation with the natural reparative processes leads to earlier healing and more complete functional recoveries than are obtainable by the orthodox procedures with prolonged fixation.

Joint Fractures.—Wilson,[45] from a study of disability records obtained from one of the state industrial boards, comprising a total of 2,106 cases, concludes that the evidence points to an unsatisfactory state of affairs in respect to the treatment of a large proportion of joint fractures. The results in terms of duration of disability are so variable in fractures of the shoulder and ankle as to indicate a strong need for a better diffusion of knowledge of approved methods of treatment, while in the regions of the elbow and knee the results are so uniformly bad as to suggest the

44 Yates, J. L., and Stevens, G. W.: Ann. Surg. **82**:617 (Oct.) 1925.
45. Wilson, P. D.: Boston M. & S. J. **193**:338 (Aug. 20) 1925.

necessity for a revision of the standard methods of treatment. In the consideration of the pathology of joint fractures, chief blame for continued disability is placed on two factors, first, the intra-articular damage with distortion of the joint surfaces resulting in articular incongruence and leading to the production of a painful traumatic arthritis, and, second, periarticular changes with adhesion of muscles and tendons by involvement in scar and callus, resulting in limitation of the range of movement. Taking up the matter of treatment, emphasis is placed upon the necessity for more complete reconstitution of the normal joint topography by open operation if necessary, and upon the early use of massage and active movement in the after-treatment, the apparatus used being selected with the view to facilitate the latter.

Ununited Fractures.—Hey Groves,[46] in a very complete article, discusses the problem of ununited fractures. The causes of nonunion are grouped as follows: I. Mechanical. 1. Gap between the bone ends. 2. Unrestricted mobility. 3. Interposition of soft parts. 4. Presence of foreign bodies. II. Vascular. 1. Sclerosis, the bone canals being closed and the cells imprisoned. 2. Atrophy with disappearance of the vital elements and persistence only of the earthy shell. 3. Sealing off the bone ends by fibrous tissue or cartilage. III. Disease. 1. Infection: pyogenic, syphilitic or tuberculous. 2. New growths: fibrocyst, myeloma, sarcoma or carcinoma.

Nonoperative and operative methods of treatment are considered in detail. Of the former, active use with brace protection of the fracture, and passive congestion with massage and injections of blood, serum or fibrin in and around the fracture are considered useful in certain cases. Emphasis is, however, laid on operative methods, the different procedures being described as "stimulation of bone ends," shaping and fitting operations, bone grafting operations and supplementary bone grafting methods (osteoperiosteal grafts). The causes of failure of operative treatment are stated to be (1) inadequate contact of bone ends; (2) inadequate fixation; (3) inadequate graft, and (4) excessive tension.

Pelvic Fractures.—Watts,[47] analyzing the end-results of forty-eight cases of pelvic fracture, concludes that fractures of the simple type are usually not serious and should not require a disability period in excess of ten or twelve weeks. The complicated fractures are always serious and require proper treatment of the complicating lesions. The period of disability is dependent on the nature and extent of the complications and is usually from four to six months. The following complications were encountered: sacro-iliac disturbances in 14.58 per cent; rupture of the bladder in 6.25 per cent; rectal tear in 4.1 per cent, and sciatic

46. Hey Groves, E. W.: Lancet **2**:735 (Oct. 10) 1925.

47. Watts, W. B.: Southwestern Med., August, 1925, p. 293.

neuritis in 2.08 per cent. He notes that the disability period is always longer in industrial cases in which compensation is expected.

Compensatory Lengthening of the Femur in Children After Fracture.—Cole [48] adds another series of cases to the thirty-one he reported a few years ago of fracture of the femur in children in which the end-results in respect to compensatory lengthening to overcome shortening occur in the majority of cases. The amount of this lengthening varies with each patient and is not dependent on any form of treatment. It may take place in the tibia as well as in the femur. Its effect is to bring the two legs to nearly equal length within two years. Abnormal bowing of the shaft is one of the greatest factors of deformity and disability and in his series was encountered only in the cases in which operation was done.

[ED. NOTE.—Cole's careful observations confirm those of other investigators which have been summarized in previous Reports of Progress. They constitute a strong argument for conservative measures in the treatment of fracture of the femur in children and against the employment of open methods even if there is overriding of fragments of as much as 1 inch (2.5 cm.).]

Fracture of the Sesamoid Bone of the Great Toe.—Delagenière [49] reports two cases of fracture of the internal sesamoid bone of the great toe, in women aged 18 and 43 years, respectively. In both cases the fractured sesamoid was removed through a small incision and the ends of the tendon were sutured together.

[ED. NOTE.—Congenital division of the sesamoid is a common condition and may easily be mistaken for fracture. Care is necessary to avoid this error. The key to the situation is often to be found in the presence of a similar condition in the opposite foot. However, even when an actual fracture is present, it by no means follows that the sesamoid must be excised. Good results have been obtained by simple fixation, while on the other hand several bad results with painful weight bearing following operative treatment have been seen by one of us.]

DISLOCATIONS

Dislocation of the Carpal Semilunar Bone.—Brandt,[50] discussing the mechanism by which dorsal dislocation of the semilunar is produced, points out that this bone is the only one of the entire carpus without muscular attachment. In falling on the extended wrist, first a rupture of the volar ligaments occurs, then a dorsal displacement of the carpus beyond the radial border, the dorsal ligaments tearing. An attempt is made to counteract this by flexing the wrist, which is successful in the

48. Cole, W. H.: Ann. Surg. **82**:609 (Oct.) 1925.
49. Delagenière, H.: Bull. et mém. Soc. nat. de chir. **51**:722 (June 27) 1925.
50. Brandt, G.: Deutsche Ztschr. f. Chir. **190**:396, 1925.

case of all the bones but the semilunar, which remains behind as an isolated dislocation.

Conwell [51] reports three cases of anterior dislocation of the semilunar bone, two being complicated by a fracture of the ulnar styloid and one by fracture of the scaphoid, in which closed reduction by the method of Davis was successfully used. A round stick the size of a broomstick is placed at the edge of a table. The volar surface of the wrist is pressed down on this so that the stick exerts pressure against the dislocated semilunar. By exerting traction on the hand while at the same time strongly hyperextending the wrist, the operator opens up the bed of the semilunar. Reduction is completed by flexing the wrist acutely while maintaining the traction. The functional end-results of these cases were practically perfect.

Fracture Dislocation of the Head of the Humerus.—Groves [52] recommends immediate open reduction of all fracture dislocations of the upper end of the humerus. The approach is made through the anterior incision with the upper end prolonged backward along the acromion. The dislocated head is replaced in the glenoid and lined up with the shaft. Occasionally internal fixation by means of an intramedullary peg is required. The after-treatment consists of fixation in the adducted position by an axillary pad and sling for the first few days, followed by abduction of the shoulder by means of an airplane splint, which is used for from four to six weeks. Massage and exercise are employed after ten days. In late neglected cases, the author recommends removal of the head, and in some cases, if the shoulder is weak, arthrodesis.

[ED. NOTE.—We also favor replacement of the head whenever possible. Removal of the head is the easy thing to do, but the functional results from replacement are immeasurably superior to those from excision. Even when the head is entirely cut off from its blood supply, there is a good chance for it to survive and recover function.]

Chronic Recurrent Dislocation of the Shoulder.—Thomas,[53] reporting the results of operation by his method of axillary capsulorrhaphy in chronic recurrent dislocation of the shoulder, states that it was successful in 66 per cent of the eighteen cases comprising the epileptic group, and in 66.5 per cent of the thirty-three cases that were traced of the non-epileptic group. In the latter group dislocation had recurred once in seven cases and twice in one case. Two cases were acknowledged failures. He does not believe that dislocation after operation necessarily means failure, especially when followed by another operation, as the cicatricial tissue that strengthens the weakened joint is made all the stronger. With this point in view he believes that his results to date show close to 100

51. Conwell, H. E.: Ann. Surg. **82**:609 (Aug.) 1925.
52. Hey Groves, E. W.: Lancet **2**:513 (Sept. 5) 1925.
53. Thomas, T. T.: J. A. M. A. **85**:1202 (Oct. 17) 1925.

per cent cures and close to 100 per cent functional results in nonepileptic patients.

The *British Medical Journal* in an editorial [54] takes issue with the foregoing statement by Thomas, and states, "his claim is a big one and we fear it is not justified by the case histories which Dr. Thomas has published." The belief is expressed that there is great weight in the arguments of Sever, who holds that although plaiting or constricting operations on the capsule have apparently been successful in a number of cases, the success was due, not to the reinforcement of the capsule, but to the necessary interference with the muscles around the joint, and in particular to the division and subsequent suture of the tendon of the subscapularis near its insertion, which is a marked feature of Thomas' operation of capsulorrhaphy.

That the operative treatment of recurrent dislocation of the shoulder is far from being standardized is shown by the constant appearance of new articles in the literature reporting fresh procedures, each with its list of successes. Thus, in the opinion of Perthes,[55] the recurrence of the dislocation is caused either by an avulsion of the capsule and muscles at the greater tuberosity of the humerus, or by tearing away of the capsule at the anterior margin of the glenoid. He operates, therefore, depending on his findings, either fixing the capsule and tendons to the greater tuberosity by a nail or by suturing the medial portion of the capsule to the glenoid with wire. He reports eleven cases in which operation had been done in this manner by himself many years previously without any recurrence. Steinmann,[56] on the other hand, recommends an operation to extend the anterior margin of the glenoid. He employs the anterior approach between the tendons of the biceps muscle. The subscapularis muscle is split longitudinally, the capsule is exposed, and the periosteum on the surface of the scapula close to the rim of the glenoid is elevated for a distance of 5 or 6 mm. A graft 6 cm. long and 1 or 1.5 cm. wide and 4 mm. thick is then taken from the tibia and inserted between the scapula and the periosteum in such a way that it projects 1 cm. beyond the border of the articular cavity. The graft is fastened with a nail or by suture with wire. This operation has also been employed by Eden.

[ED. NOTE.—The mere fact that so much controversy exists is to us the best proof that the causative factors underlying habitual dislocation of the shoulder are not yet completely understood. Operations that are designed to correct or remove the etiologic factors are therefore fallacious. Knowing the strength and permanent character of transplanted fascial cords, we are of the opinion that such structures properly

54. Editorial, Brit. M. J. Nov. 14, 1925, p. 911.
55. Perthes, G.: Zentralbl. f. Chir. **52**:2195, 1925.
56. Steinmann, F.: Schweiz. med. Wchnschr. **55**:470 (May 28) 1925.

employed, as in the operation devised by Plummer, offer the greatest hope of permanently preventing dislocation.]

AMPUTATIONS

Little,[57] whose great experience with prosthetic appliances for amputation cases is well known, describes a new principle in leg fitting which may prove of great service, especially in the case of short thigh stumps. The socket is made of duralumin and is fitted closely to the bare stump, with the exception of a space free from pressure at the end. The socket is grooved horizontally close to its top, the groove being 1⅛ inch (2.8 cm.) wide and one-eighth inch (0.3 cm.) deep. The socket is air tight, and when the stump is forced in, the air is exhausted and a partial vacuum and suction is created which holds the apparatus in place. A spring valve is fitted to the socket, through which the air may be admitted when it is desired to remove the leg. The suction force is great and the leg remains securely in place without the necessity of suspenders. Attempts to pull off the leg by main force without opening the valve failed in all cases, and an illustration is shown in which the patient is suspended head downward by the leg. The device has been in use on eleven patients for periods varying from two months to two years, and during this time no bad effects on the skin from the lack of ventilation or tight fit have been seen.

BODY MECHANICS

Anatomic Considerations.—Adams[58] feels that the regions of the spine in which the strains most commonly occur are those in which because of the anatomy the mechanics are such that there is the greatest possibility of strain. These regions are, first, the low cervical region, where there is so commonly seen the hump in round, hollow backed women. Strains in the thoracic region are not common. The dorsolumbar region, one of the most limber spinal sections, is frequently strained, chiefly in the round, hollow backed type of person. There are but few patients who have symptoms that can be attributed to the midlumbar region. The lumbosacral junction is the point at which the base of the flexible mast joins the more rigid pelvis. The pelvis is a bony ring encircling the base of the spine, and in it and to it the spine is slung and stayed by its ligaments and muscles. Hung on the articular facets of the sacrum, the fifth lumbar swings to the left when the spine bends to the right, and its wedge shaped centrum in so doing acts as an equalizer in that it evenly distributes the stress brought on the top of the sacrum. The normal average inclination of the facets on the top of the sacrum is 45 degrees. The hollow backed posture may greatly

57. Little, E. M.: Brit. M. J. **2**:896 (Nov. 14) 1925.
58. Adams, Z. B.: J. A. M. A. **85**:247 (July 25) 1925.

increase this pitch, in which position the prop of the top of the sacrum is proportionately taken out from under the spine, and the stress is thus made greater on the slings, the iliolumbar ligaments. Under treatment, Adams says that the ability to hold the back in the best position to avoid strains certainly depends to a large degree on how the body trunk is poised on the feet, knees and hips. He reports two specimens showing congenital defective fifth lumbar vertebrae, and says that if back symptoms seem to have developed from this condition, locking of this section by bone graft or fusion is necessary to get permanent relief.

[ED. NOTE.—These correct anatomic observations of Adams have point because we believe they are less commonly visualized by the rank and file of examining physicians than they ought to be. Every machine, the human machine included, is subjected to stress and strain. All good machines have a margin of safety and there are danger zones as well. We must know the details of construction before we can estimate these margins of safety and these danger zones. When the body is habitually used in attitudes that make it impossible to satisfy the mechanics of its construction, wear is sure to occur. Its efficiency is lessened and the life of the machine is shortened. It behoves us to pay more attention to these human machines and to understand more completely their construction, for without this understanding we shall be unable to calculate accurately the normal and safe stresses and strains and correct those which are abnormal and must be dangerous.]

Back Strain.—Simmons and Clark,[59] in a review considering the economic aspects of back strain, say that back strain is important to the industrial physician and surgeon because of its prevalence; to the employer because of time lost in production and the cost of compensation. They believe that the number of back strain patients unable to return to work is small. Although back strain is frequently a disabling accident when it occurs, the disability is not as a rule permanent. Practically all the men were able to do regular work again and the majority were working in the same department as they were before injury. Prolonged and complete disability is in most cases due to some complicating disease of the spine.

Orthostatic Albuminuria.—Russell,[60] after a five years' study of orthostatic albuminuria, comes to the conclusion that some response to posture occurs in most cases of nephritis, and possibly in all forms of albuminuria. All degrees of diminution of the output of albumin during rest in bed are met with, down to the complete cessation in the typical orthostatic case.

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59. Simmons and Clark: J. Indust. Hyg., September, 1925.
60. Russell: Lancet **2**, Sept. 3, 1925.

RESEARCH

Twenty Years' Research in Transplantation.—Lexer [61] reviews his experiments and clinical experience. Regeneration takes place by so-called creeping restitution and absorption. In a soft tissue bed, periosteum and endosteum are indispensable. Moreover, the periosteum and endosteum are protective and nutritive membranes that prevent absorption of the bone surface. In favorable healing of an autoplastic graft, the following stages may be differentiated: the stage of atrophy, when absorption prevails with vascularization and diminution of lime salts; the stage of living transformation, beginning at the third or fourth month (in grafts for defects of the skull not before the twelfth month); the stage of functional transformation, beginning after the fourth month and leading to changes in size and shape of the graft. In a similar way, pathologic changes in the graft may be distinguished: absorption by granulation tissue; fractures of the graft, which may take place during the fourth month because resistance is diminished; fractures that often occur as creeping fractures, which means a gradual solution. The healing of fracture of a graft is brought about by the tissues of the bony bed. Lexer does not believe in metaplasia. Homoplastic grafts are not suitable for soft tissue beds, but require bony beds, in which they develop stronger reaction than autoplastic grafts. Heteroplastic grafts are usually absorbed or cast off as foreign bodies. The best time for grafting fractures is the second week after the break. Lexer reports the fate of transplanted whole joints, and states that both mobility and weight bearing are good after many years of observation. There is change in contour two years after the operation, due to the compression of the necrotic central parts. Transplantation of half joints gave better results than transplantation of whole joints.

Calorimetric Studies of the Extremities Following Lumbar Sympathetic Ramisection and Ganglionectomy.—Brown and Adson [62] have made a study of the vasomotor effects of ramisection on the extremities. Five cases of spastic paralysis are reported, in which bilateral lumbar sympathetic ramisection and ganglionectomy were performed. The second, third and fourth lumbar ganglions, with the sympathetic trunk, were removed, and the rami divided. During the postoperative period marked increase in the skin temperature of the legs and feet was observed. Calorimetric studies demonstrated marked increased heat production and heat radiation. There was complete absence of sweating in the legs in two cases.

The Relation of the Bone Marrow to the Lymphatic System: Its Rôle in the Spreading of Carcinomatous Metastases Throughout the

61. Lexer, E.: Arch. f. klin. Chir. **138**:251, 1925.
62. Brown, G. E., and Adson, A. W.: Am. J. M. Sc. **170**:232 (Aug.) 1925.

Skeleton.—Kolodny,[63] by experiments that have been carried on chiefly in the long bones of dogs in which carmine or India ink was injected into the medullary cavities, reaches the following conclusions: The bone marrow is directly related to the lymphatic system; it drains its lymph into certain groups of lymph nodes which are regional lymph nodes of the respective bone. The regional lymph nodes of the bones of the lower extremity are the iliac lymph nodes in dogs, corresponding to the external chain of the iliac group and the hypergastric lymph nodes in man; the direct relationship existing between the bone marrow and the lymphatic system forms the anatomic basis for the lymphogenous theory of the metastatization of carcinomatous tumors to the bones.

The Reformation of Synovial Membrane in the Knees of Rabbits After Synovectomy.—Key [64] has studied the results of synovectomy of the mesial side of the knee joint in twenty-four rabbits. His studies picture a joint filled with a mixture of blood and synovial fluid. A clot of cells and fibrin adheres to the denuded surface. There is an immediate polymorphonuclear leukocyte reaction that lasts about forty-eight hours, and then the polymorphonuclears disappear and phagocytes wander into the joint. Capillaries grow into the fibrin, and by the sixth day it is fairly well organized. By the fourth day a definite surface zone on the adherent fibrin is demarcated by a thin hyaline layer which stains like collagenic tissue. This surface zone for a time is not penetrated by the advancing fibroblasts, but they form a layer just beneath it. As the clot becomes organized, the fibrin and extravasated blood are absorbed, and by the tenth day a few collagenic fibers are present. These are rapidly increased during the next five days. Mitotic figures are frequent, and the proliferation of fibroblasts continues until about the fifteenth day. At this time the fibrin has almost entirely disappeared. The denuded area is now covered by a thick, highly cellular layer of loose fibrous tissue which is vascular, and has a well defined surface layer of fibroblasts. This membrane of young connective tissue now slowly matures to form a synovial lining that can be distinguished only with difficulty from that of a normal joint. As the fibroblasts decrease in size and number, collagenic fibers are laid down. The surface or synovial cells are decreased in size and number and become flattened. They lie not on the surface but in the surface, as is true of normal synovial membrane. Joints are not lined by a layer of mesothelium, but their lining is a connective tissue surface made up of cells and collagenic tissue. In the rabbit, the joint is again approximately normal sixty days after hemisynovectomy. The new synovial membrane is formed in situ by metaplasia of underlying connective tissue cells. There is little or no

63. Kolodny, Anatole: Arch. Surg. **11**:690 (Nov.) 1925.
64. Key, J. A.: J. Bone & Joint Surg. **7**:793 (Oct.) 1925.

tendency for surface growth from the edges to cover the denuded area as occurs in the repair of a defect in an epithelial surface. The synovial cells are connective tissue cells specialized by their location.

Cultivation of Periosteum Explants: Rôle of Perichondrium in Formation of Bone and Cartilage.—Policard and Boucharlat [65] found exclusively connective tissue cells in explant cultures of periosteum and perichondrium from mammals. Evidently the formation of bone and cartilage is due not only to the periosteum and perichondrium, but it also involves certain humoral actions, which are lacking in test tube cultures.

A Roentgen-Ray Study of the Injected Knee Joint.—Colp and Klingenstein,[66] in observations on fifty patients injected solutions of sodium iodide and air, in equal parts, into nearly a hundred knee joints. By the roentgenograms they have been able to demonstrate the limits of the joint spaces in flexion and extension, and to show that the extent of the suprapatellar bursa (which in every case communicated with the joint) is greater than anatomists have generally described it, extending to 10 or 12 cm. above the patella. Their findings have definite bearing in the Willems treatment for suppurative processes, as it is evident that motion certainly drains all compartments of the joint.

MISCELLANEOUS

Osteitis Fibrosa and Hyperostotic Form of Bone Syphilis.—The primary purpose of Wilhelm's [67] investigation is to establish the differential diagnosis between the hyperostotic form of bone syphilis and osteitis fibrosa. There are gross anatomic and clinical resemblances between the hyperostotic form of syphilis of the long bones and the osteitis fibrosa, both being the senile hyperostotic-porotic form. Coarser gross morphologic similarities, such as deformities, elongation and bowing, and especially the sabre blade form of tibia, are found in the affected bones of both diseases. Despite these external similarities, we are dealing with two fundamentally different diseases, especially in regard to their histogenesis. Characteristic of hyperostotic syphilis are (*a*) the marked, often tremendous, participation of the periosteum; (*b*) the more or less advanced narrowing and obliteration of the marrow cavity, and (*c*) the sclerotic or finely porous quality of the newly built bone tissue. The spaces or pores, particularly in the roentgenograms, seem to be directed lengthwise, parallel to the long axis of the diaphysis. The sabre blades

65. Policard, A., and Boucharlat, M.: Compt. rend. Soc. de biol. **92**:533 (May 22) 1925.

66. Colp, Ralph; and Klingenstein, Percy: Arch. Surg. **11**:660 (Nov.) 1925.

67. Wilhelm, S. F.: Surg. Gynec. Obst. **41**:624 (Nov.) 1925.

of the senile hyperostotic-porotic form of osteitis fibrosa show (*a*) the absence of periosteal participation; (*b*) the great widening of the marrow cavity, even into the epiphyses, and (*c*) the frequent lengthwise splitting up of the compacta into lamellae. The sabre blade tibia of Paget's disease is the result of the rebuilding and elongation of the bone, i. e., a true bowing. In the juvenile endosteal hyperostotic-porotic form of osteitis fibrosa there is also a complete absence of periosteal involvement. Only the latter cases may be difficult to distinguish roentgenologically from congenital bone syphilis. The occurrence of more or less well formed cysts, or of single, circumscribed, dense foci accompanying a diffusely spreading osteitic new bone formation, are diagnostic points in favor of osteitis fibrosa as against syphilis.

Apparent Destruction of Bone in the Roentgen-Ray Picture of Perthés' Disease and Allied Conditions.—Friedrich [68] thinks that the roentgen-ray picture of such alterations of the bone as Perthés disease, the unexplained changes seen occasionally in the semilunar bone, etc., may give a wrong idea of the actual microscopic changes. At several operations performed in such cases in which he had expected to find a much changed bone, he found only slight apparent changes.

[Ed. Note.—Some of us have confirmed these experiences of Friedrich. In two exploratory operations on the hip joint in supposed Legg's disease, with a roentgenologic appearance of marked pathologic changes in the bone and osseous center, the appearance of the joint surface in structure and shape revealed at operation would have easily passed for normal.]

The Prostate and Its Influence on Low Back Pain.—From an examination of the histories of 100 cases in which the routine urologic history had included in it the question of backache, Player [69] makes the statement that one of the most important causes of backache in man is prostatitis. Routine examination of the prostate gland should be made in all patients complaining of backache.

Manipulative (Chiropractic) Dislocations of the Atlas.—Blaine [70] reports three cases in which evidence is presented of dislocations apparently produced by chiropractors through their so-called spinal adjustments or replacements to relieve supposed pressure on a nerve. To treat a heart lesion resulting from an acute exanthem, or an inflammatory joint disease by replacing a supposedly dislocated vertebra said to have caused the abnormal condition seems to the author preposterous. So long as the laws governing the health of the individual permit such

68. Friedrich, H.: Deutsche Ztschr. f. Chir. **191**:40, 1925.
69. Player, L. P.: California & West. Med. **23**:993 (Aug.) 1925.
70. Blaine, E. S.: J. A. M. A. **85**:1356 (Oct. 31) 1925.

methods as those employed by chiropractors to be practiced, just so long will occurrences such as those detailed in this presentation take place, and the unsuspecting public remains unprotected.

BOOK REVIEWS

A Textbook of Operative Orthopedics. By A. Steindler, M.D., F.A.C.S., Professor of Orthopedic Surgery, State University of Iowa. New York: D. Appleton & Co., 1925.

This profusely illustrated book by Steindler is an important contribution to orthopedic surgery. In it one may find not only the working outlines of most of the important bone, joint and tendon operative procedures whose end-results justify their performance in suitable cases, but also in most instances the author's evaluations and the statistics of his own cases. We would wish for an even more extended discussion of these procedures by Steindler, for his experience is large, his review of cases most conscientious, and his judgment mature and reliable. By the laws of the state in which his clinic is conducted, it is possible for him to study his end-results carefully and constantly. Only by such study and by careful selection of suitable cases can the lasting merit of an operative procedure be determined. We commend the book most highly to all those interested in bone and joint and locomotive surgery.

Treatment of Tuberculosis of the Hip. By G. R. Girdlestone. New York: Oxford University Press, 1925.

Girdlestone has succeeded in writing an authoritative textbook which is really pleasant reading. It is a small book on a single important subject and there is much information and much food for thought in its less than a hundred pages. The author's training has been thorough, his experience wide, his observation keen, his judgment sound, and his enthusiasm great. He writes of this crippling condition with much sympathy and understanding and he writes well. The illustrations are excellent and all have point. The little book is a distinct addition to medical literature, and should be read by all those who essay to treat tuberculosis of the bones and joints.

Scoliosis, Rotary Lateral Curvature of the Spine. By Samuel Kleinberg, M.D., F.A.C.S. Dedicated to Dr. Royal Whitman, New York: Paul B. Hoeber, 1926.

It requires courage to write a book on scoliosis, or rotary lateral curvature of the spine, for, as the author frankly states, neither its etiology nor its mechanics are clearly understood, and the complete cure of a severe case with a fixed rotation and angular rib deformity is almost unknown. There is much of value in Kleinberg's book. He draws a strong and appealing picture of the mental distress that this painless bodily deformity often causes, pleading for early recognition and early treatment. He honestly tells us how much or how little we may expect from treatment and describes the methods that in his large experience have yielded the best results. It is evident that there must be other causes than faulty postures and congenital vertebral variations to account for the severe, progressive, fixed structural types, else every case of short leg from hip disease or infantile paralysis would develop it, and they do not. The author thinks that Buchman

may have suggested it in the obscure condition known as vertebral epiphysitis. In the section on anatomy and physiology the author closely follows the teaching of Lovett. He considers the early results of correction in recumbency followed by ankylosing operations on the spine to be full of promise. The rôle that gymnastic exercises should play in the treatment of the disease is emphasized and the various types of exercise are clearly described with photographs and line drawings. The book of 300 pages is excellently printed and illustrated.

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